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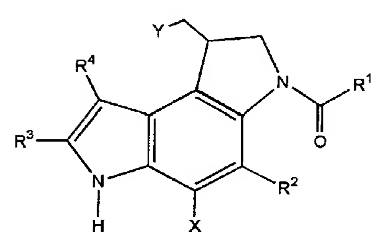
(54) Title: PYRROLO-INDOLE AND PYRROLO-QUINOLINE DERIVATIVES AS PRODRUGS FOR TUMOUR TREATMENT



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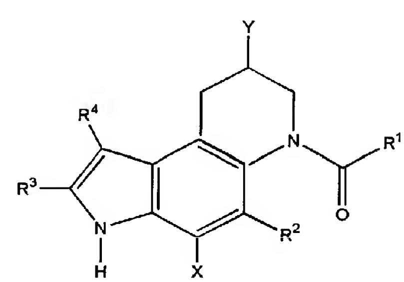


(IA)

(57) Abstract: Compounds of the general formula (I) or (IA) in which X is H, Y is a leaving group, R^1 and optionally also R^3 preferably being an aromatic DNA binding subunit are prodrug analogues of duocarmycin. The compounds are expected to be hydroxylated at the carbon atom to which X is joined, by cytochrome P450, in particular by CYP1B1, expressed at high levels in tumours. The prodrug is expected to be activated preferentially in tumour cells, where it will act as a DNA alkylating agent preventing cell division.

WO 02/068412 A1

PYRROLO-INDOLE AND PYRROLO-QUINOLINE DERIVATIVES AS PRODRUGS FOR TUMOUR TREATMENT

The present invention concerns aromatic oxidation/hydroxylation activated prodrugs, particularly anti-tumour prodrugs and those which are specifically activated by the oxidation/hydroxylation activities of the cytochrome P450 family of enzymes.

Many conventional cytotoxic drugs are known that can be used for therapeutic purposes. However, they typically suffer from the problem that they are generally cytotoxic and therefore may affect cells other than those that are required to be destroyed. This can be alleviated to some extent by the use of targeted drug delivery systems, for example direct injection to a site of tumourous tissue or, e.g. binding the cytotoxic agent to an antibody that specifically recognises an antigen displayed only on the cancer cell surface. Alternatively, electromagnetic radiation may be used to cause chemical alteration in an agent at a desired site such that it becomes cytotoxic. However, all of these techniques have, to a greater or lesser extent, certain limitations and disadvantages.

The compound (+)-CC-1065 and the duocarmycins are naturally occurring representatives of a class of DNA alkylating agents. The naturally occurring compounds consist of a DNA alkylating unit based upon a pyrrolo[3,2-*e*]indole core, with one or two sub units, conferring DNA binding capabilities. CC-1065 and duocarmycin A comprise a spirocyclic cyclopropane group responsible for the DNA alkylation properties. Duocarmycin B_2, C_2 and D_2 are believed to be precursors for cyclopropane actives, and comprise a substituted (by a leaving group) methyl group at the eight position on the dihydro pyrrole ring. CC-1065 has been synthesised by various routes, summarised by Boger *et al* in Chem. Rev. 1997, 97, 787-828.

In US-A-4413132 the first synthesis of the left hand sub-unit of CC-1065 was described. The synthesis is based on a Winstein Ar-3' alkylation in which the cyclopropane ring is introduced. In a previous step, the A ring (of the indole core) is introduced by reaction of an aniline with an α-thiomethylester using chemistry based on Gassman's Oxindole synthesis. The aniline has a protected phenolic hydroxyl group ortho to the NH_2 group,

which, in the final product, is believed to be crucial for DNA alkylation. CC-1065 has broad antitumour activity but is too toxic against normal cells to be clinically useful. Attempts have been made to target the delivery of CC-1065 and analogues by conjugating the drug via the DNA binding subunit to polymers, or specific binding agents such as antibodies or biotin described in US 5,843,937. Boger *et al* in Synthesis 1999 SI, 1505-1509 described prodrugs of 1,2,9,9a-tetrahydrocyclopropa(c)benz[e]indol-4-one, in which the cyclopropane ring-opened version of the compounds were derivatised by reaction of the phenolic group to form esters and carbamates.

In J.Am.Chem.Soc. (1991), 113, 3980-'83 Boger *et al* describe a study to identify features of CC-1065 analogues contributing to the selectivity of the DNA-alkylation. The compounds tested *in vitro* had alkylating subunits based on 2,3-dihydroindole and included the 6-deshydroxy analogues. These were shown to have some DNA alkylating properties though at concentrations 10^4 times higher than that of the 6-hydroxy compounds.

Tercel *et al*, in J. Org. Chem. (1999) 64, 5946-5953 describe amino analogues of CC-1065 (i.e. in which the phenolichydroxy of the B-ring is replaced by amino). These are synthesised by nitrating the benzene ring in a late stage intermediaet having a methylol group attached to the dihydropyrrole ring.

The present invention relates to precursors of CC-1065 and its analogues, which do not have the hydroxyl group in the B ring of the alkylating sub unit, and which are hence inactive as DNA alkylating agents themselves, as well as their synthesis and intermediates used therein.

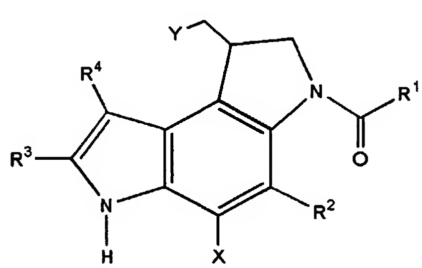
It has been reported (Murray, G.I. *et al.*, 15 July 1997, Cancer Research, 57m 3026-3031 and WO-A-9712246) that the enzyme CYP1B1, a member of the cytochrome P450 (CYP) family of xenobiotic metabolising enzymes, is expressed at a high frequency in a range of human cancers, including cancers of the breast, colon, lung, oesophagus, skin, lymph node, brain and testes, and that it is not detectable in normal tissues. This led to the conclusion that the expression of cytochrome P450 isoforms in tumour cells provides a molecular target for the development of new antitumour

drugs that could be selectively activated by the CYP enzymes in tumour cells, although no drug examples were given. A number of other CYP isoforms have been shown to be expressed in various tumours. Many of the CYP's expressed in tumours are mentioned in Patterson, LH *et al*, (1999) Anticancer Drug Des. 14(6), 473-486.

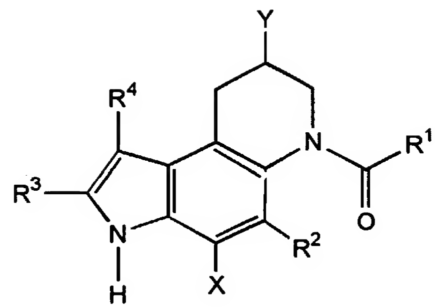
In WO-A-99/40056 prodrugs of styrene- and chalcone-derivatives are described. The respective hydroxylated forms of the prodrugs, formed *in situ*, are potent tyrosine kinase (TK) inhibitors. Inhibition of TK activity contributes to tumour inhibition and cell destruction. The prodrugs were shown to be activated by microsomal preparations expressing CYP1B1 enzyme, and to have cytotoxic activity against cell lines expressing the same enzyme, whilst having much lower cytotoxic activity against cell lines not expressing the enzyme.

The present invention is directed to a new class of prodrugs which are expected to be hydroxylated *in situ* by CYP enzymes, in particular enzymes expressed at high levels in tumours as described in Patterson LH, *et al*, *op. cit.*. In particular the prodrugs are believed to be metabolisable by CYP1B1 enzyme. Some of the compounds are new. The present invention relates to the first therapeutic use of a broad range of compounds.

There is provided according to the first aspect of the invention the new use of a compound of the general formula I or a salt thereof in the manufacture of a composition for use in a method of treatment by therapy of an animal:



I



IA

in which X is H;

Y is a leaving group

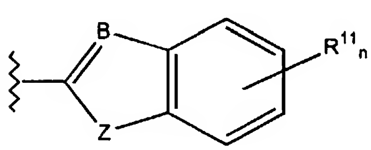
R^1 is -Ar, $-NH_2$, R^8 or OR^8;

R^2 and R^4 are each independently selected from H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, -CN, Cl, Br, I, $-NO_2$, $-NH_2$, $-NHCOR^9$, $-NHCOOR^9$, -COOH, $-CONHR^9$ and $-COOR^9$;

R^3 is selected from H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, -CN, Cl, Br, I, $-NO_2$, $-NH_2$, $-NHCOR^9$, $-NHCOOR^9$, -COOH, $-CONHR^9$, $-COOR^9$ and $COAr^{10}$;

R^8 and, R^9 are independently selected from C_{1-4} alkyl, optionally substituted phenyl, C_{7-12}-aralkyl, optionally substituted heteroaryl and ligands;

Ar is selected from



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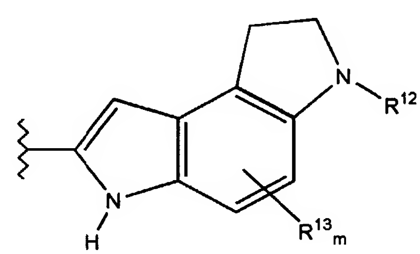

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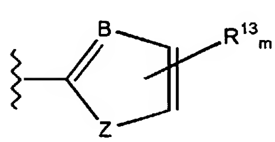

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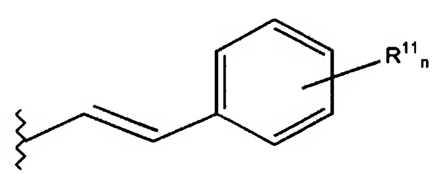


in which B is N or CR^{14};

Z is O, S -CH=CH- or NH;

the or each R^{11} is selected from OH, C_{1-4} alkoxy, C_{1-4} alkyl, $-NO_2$, $-NH_2$, $-NHR^{10}$, $-NR^{10}_2$, $-N^+R^{10}_3$, -CN, Cl, Br, I, $-NHCOR^{15}$, -COOH, $-CONHR^{16}$, $-NHCOOR^{16}$ and $COOR^{16}$;

n is an integer in the range 0 to 4;

the or each R^{10} is selected from C_{1-4} alkyl, optionally substituted phenyl, C_{7-12}-aralkyl, optionally substituted heteroaryl and ligands;

R^{12} is H, $-COAr^1$, $-CONH_2$, -COOH, $-COR^{16}$ or $-COOR^{16}$;

the or each R^{13} is selected from OH, C_{1-4} alkoxy, C_{1-4} alkyl, $-NO_2$, $-NH_2$, $-NHR^{10}$, $-NR^{10}_2$, $-N^+R^{10}_3$, -CN, Cl, Br, I, $-NHCOR^{15}$, -COOH, $-CONHR^{16}$, $-NHCOOR^{16}$ and $-COOR^{16}$;

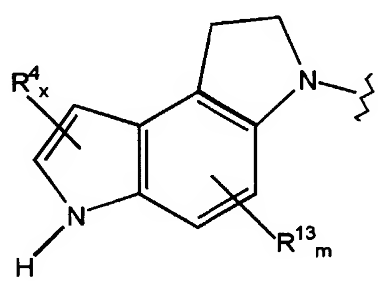
m is 0, 1 or 2;

R^{14} is selected from OH, C_{1-4} alkoxy, C_{1-4} alkyl, $-NO_2$, $-NH_2$, -CN, Cl, Br, I, $-NHCOR^{15}$, -COOH, $-CONHR^{16}$, $-NHCOOR^{16}$ $-COOR^{16}$ and H;

R^{15} is selected from C_{1-4} alkyl, optionally substituted phenyl, optionally substituted heteroaryl, C_{7-12} aralkyl, Ar^1 and ligands;

R^{16} is selected from C_{1-4} alkyl, optionally substituted phenyl, C_{7-12}-aralkyl, optionally substituted heteroaryl and ligands;

Ar^{10} is



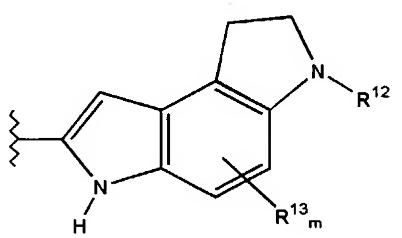
in which x is 0, 1 or 2;

Ar^1 is selected from the same groups as Ar; provided that no more than one group R^{11} or R^{13} in any one ring includes a group Ar^1.

The animal which is treated is generally a human, although the compounds may also have veternary use. The indication treated is generally cancer, including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers

of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus. The tumour may, for instance, be defined as a tumour expressing high levels of CYP1B1.

In the invention a group Ar^1 is preferably



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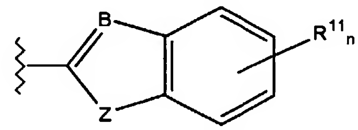


In the invention, the leaving group Y is, for instance, a group which has utility as a leaving group in nucleophilic substitution reactions. Suitable examples of such groups are $-OCOOR^5$, $-OCONHR^6$, Cl, Br, I, or $-OSOOR^7$, in which R^5, R^6 and R^7 are independently selected from C_{1-4} alkyl, optionally substituted phenyl, C_{7-12}-aralkyl and optionally substituted heteroaryl. Most preferably the leaving group is a halogen atom, preferably chlorine.

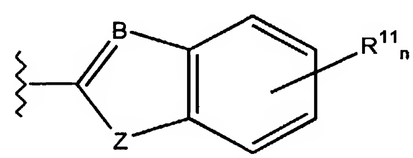
Optional substituents in phenyl, aralkyl and heteroaryl groups are, for instance, C_{1-4}-alkyl, halogen, hydroxyl, C_{1-4}-alkoxy, $-NH_2$, $-NHR^{10}$-, $-NR^{10}{}_2$, $-N^+R^{10}{}_3$, $-NO_2$-, -CN, -COOH, $-NHCOR^{15}$, $-COOR^{16}$, $-NHCOOR^{16}$ $CONHR^{16}$ etc.

In the present invention the term ligand includes a group having specific targeting characteristics, useful for instance in antibody or gene-directed enzyme prodrug-type environments. A ligand may be an oligopeptide, biotin, avidin or streptavidin, a polymeric group, an oligonucleotide or a protein. Preferably it has specific binding characteristics such as an antibody or fragment, an antigen, a sense or anti-sense oligo-nucleotide, or one of avidin, streptavidin and biotin, that is it is one component of a specific binding pair. Alternatively it may be a group designed for passive targeting, such as a polymeric group, or a group designed to prolong the stability or reduce immunogenicity such as a

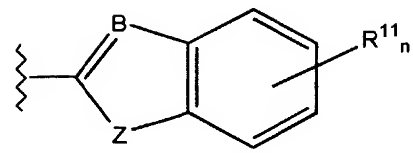
hydrophilic group. US-A-5843937 discloses suitable ligands for conjugating to these types of actives and methods for carrying out the conjugation.

In a pharmaceutically active compound R^1 is other than OR^8. In general, for optimised DNA binding ability, the group R^1 in a compound of the general formula I and IA is a group Ar and/or the group R^3 is a group Ar^{10}. Often the group R^1 may include two aromatic groups joined to one another. In such compounds, one of the groups R^{11} of the Ar group, or the group R^{12}, as the case may be, is a group Ar^1. Whilst for some compounds it may be desirable for three or more such aromatic groups to be linked, it is preferred that there is one group Ar and either one group Ar^{10}, or, more preferably, one group Ar^1. Thus in a group Ar^1 which is a pyrrolo-dihydroindole type of group, the group R^{12} should be other than a group $-COAr^1$. In a group Ar^1 which is one of the other types of group there should either be no substituents R^{11}, or R^{13} as the case may be, or, if there are any substituents, such substituents should not include a group Ar^1.

According to one embodiment of the invention, the substituent Ar is a group

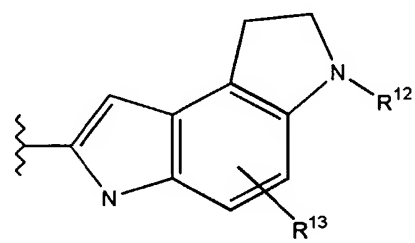


In such groups Ar, B is preferably CR^{14}. R^{14} is preferably H. The definition of Z is preferably NH, although furan (Z is O) and thiophene (Z is 5) analogues had been generated for conjugation to DNA alkylating units and may have useful DNA binding characteristics. Similarly, in a group Ar^1, the groups B and Z are selected amongst the same preferable groups. Preferably n is at least 1 and one of the groups R^{11} is $-NHCOAr^1$. In this embodiment Ar^1 is preferably a group



in which B and Z are the same as in Ar.

In another embodiment the substituent Ar is a group



Preferably R^{12} in such a group Ar is a group -COAr^1 in which Ar^1 preferably is the same type of group. Alternatively R^{12} in such a group is other than -COAr^1 and R^3 is -COAr^{10}.

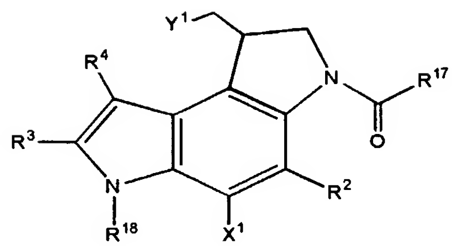
In both groups Ar and Ar^1, m in the indole type group is preferably zero.

In Ar and Ar^1, there may be several substituents R^{11}. Most preferably such substituents are selected amongst C_{1-4}-alkoxy groups.

In compounds of the formula I, the core indole ring of the DNA alkylating sub-unit is preferably unsubstituted in the benzene ring (R^2 is hydrogen), whilst the pyrrole ring may be unsubstituted (R^3 and R^4 are both hydrogen, or one or both of them represents a group -COOR^{10}, or a C_{1-4}-alkyl, preferably methyl).

In the compounds of the formula I, X is H. It is believed that, hydroxylation of the compound will occur *in situ* at the carbon atom to which X is attached, thereby activating the compound enabling it to act as a DNA alkylating agent.

Many of the compounds of the general formula I and IA, as well as amine protected precursors thereof are believed to be novel compounds. According to a further aspect of the invention there is provided a new compound of the general formula II or IIA or a salt thereof



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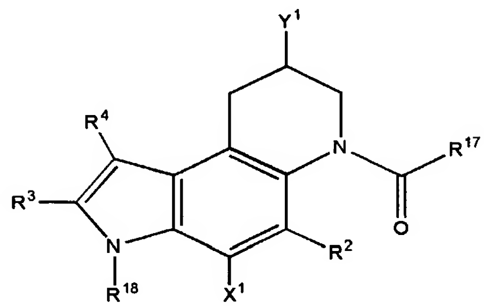


IIA

in which R^2, R^3 and R^4 are as defined for formula I and IA above;

X^1 is H;

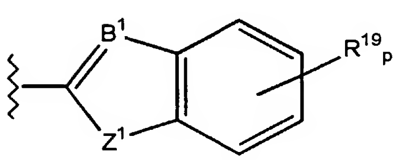
Y^1 is a leaving group;

R^{18} is H or an amine protecting group;

R^{17} is R^8, $-OR^8$ $-NH_2$ or Ar^2;

R^8 is as defined above for formula I and IA;

Ar^2 is selected from



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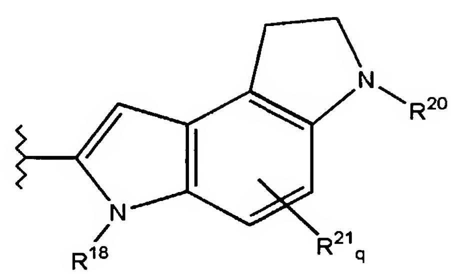

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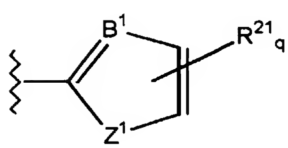

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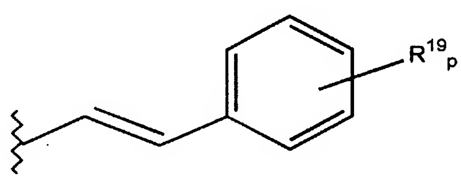


in which B^1 is N or CR^{40};

R^{40} is selected from H, OH, C_{1-4}-alkoxy, C_{1-4}-alkyl, $-NO_2$, $-NH_2$, -CN, Cl, Br, I, $-NHCOR^{22}$, -COOH, $-CONHR^{23}$, $-NHCOOR^{23}$ and $-COOR^{23}$.

Z^1 is O, S, -CH=CH- or NR^{18};

the or each R^{19} is selected from, OH, C_{1-4} alkoxy C_{1-4} alkyl, NO_2, $-NHR^{18}$, $-NHR^{23}$, $-NR^{23}_2$, $-N^+R^{23}_3$, -CN, Cl, Br, I, $-NHCOR^{22}$, -COOH, -$CONHR^{23}$ and $-COOR^{23}$;

p is an integer in the range 0 to 4;

R^{20} is H, $-COAr^3$, $-CONH_2$, -COOH, $-COR^{23}$ or $-COOR^{23}$;

the or each R^{21} is selected from OH, C_{1-4} alkoxy C_{1-4} alkyl, NO_2, $-NHR^{18}$, $-NHR^{23}$, $-NR^{23}_2$, $-N^+R^{23}_3$, -CN, Cl, Br, I, $-NHCOR^{22}$, -COOH, -$CONHR^{23}$ and $-COOR^{23}$;

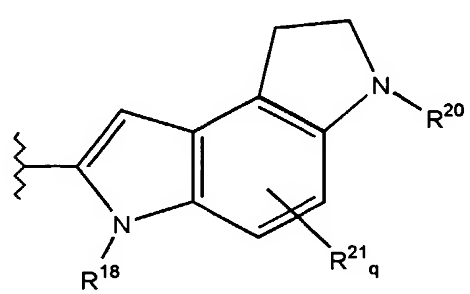
q is 0, 1 or 2

R^{22} is selected from C_{1-4} alkyl, optionally substituted phenyl, optionally substituted heteroalkyl, C_{7-12} aralkyl, ligands and Ar^3

R^{23} is selected from C_{1-4} alkyl, optionally substituted phenyl, C_{7-12}-aralkyl and optionally substituted heteroaryl; and

Ar^3 is selected from the same groups as Ar^2 provided that no more than one R^{19} or R^{21} in any one ring includes a group Ar^3.

Ar^3 is preferably.



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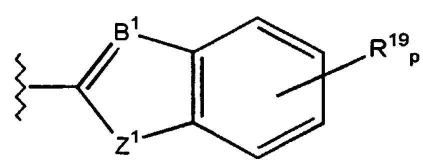


Compounds of the formula II or IIA, in which primary or secondary amine nitrogen atoms are protected are generally deprotected before being used in pharmaceutical compositions. Examples of amine protecting groups are benzyl, benzyloxycarbonyl, tertiary butyloxycarbonyl (BOC), fluorenyl-N-methoxy-carbonyl (FMOC) and 2-[biphenylyl-(4)]-propyl-2-oxycarbonyl. In particularly useful services of compounds of the general formula II and IIA

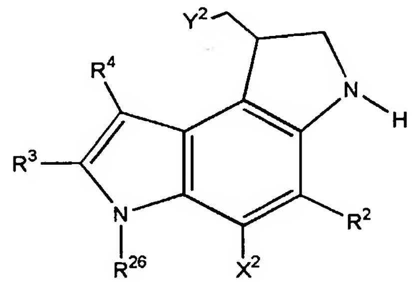
R^{17} is -OR^8 and R^8 is an amine protecting group different to R^8OCO-. In another preferred services R^{17} is other than DR^8. Where more than one such amine group is protected in the molecule, the protecting groups may be the same or different.

The present invention further provides pharmaceutical compositions comprising compounds of the formula I or IA or salts and a pharmaceutically acceptable excipient. Pharmaceutical compositions may be suitable for intramuscular, intraperitoneal, intrapulmonary, oral or, most preferably, intravenous administration. The compositions contain suitable matrixes, for example for controlled or delayed release. The compositions may be in the form of solutions, solids, for instance powders, tablets or implants, and may comprise the compound of the formula I in solid or dissolved form. The compound may be incorporated in a particulate drug delivery system, for instance in a liquid formulation. Specific examples of suitable excipients include lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate. Solid compositions may take the form of powders and gels but are more conveniently of a formed type, for example as tablets, cachets or capsules (including spansules). Alternative, more specialised types of formulation including liposomes, nanosomes and nanoparticles.

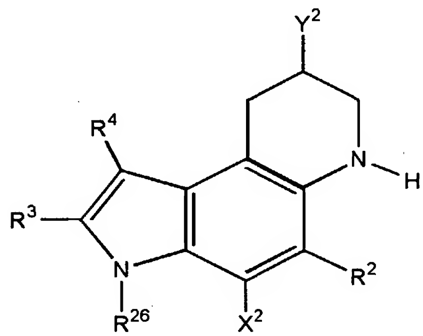
Compounds of the formula I and IA may be synthesised using techniques analogous to those summarised by Boger *et al* 1997, *op. cit.* It is convenient to form the DNA alkylating sub unit in one series of steps and to attach this through the nitrogen atom of the dihydro-pyrrole or tetrahydroquinoline, as the case may be, (C) ring to the rest of the molecule. The DNA alkylating sub-unit may be conjugated to DNA binding sub-units synthesised as described in Boger *et al*, 1997 *op. cit.*, for instance the PDE-I

and PDE-II sub-units described in that reference. The DNA binding subunits are the groups including Ar, Ar^1 and Ar^{10}.

According to a further aspect of the invention there is provided a new synthetic method in which a compound of the formula IV or IVA



IV



IVA

in which X^2, R^2 and R^4 are as defined above;

R^{37} is selected from the same groups as R^3;

Y^2 is a leaving group or a hydroxyl or protected hydroxyl group; and

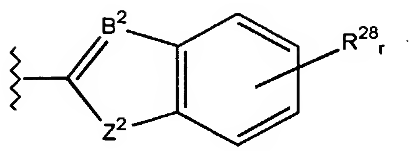
R^{26} is an amine protecting group;

is reacted with a compound of the general formula V

$$R^{27}COY^3 \qquad V$$

in which R^{27} is selected from C_{1-4}-alkyl, optionally substituted phenyl, C_{7-12}-aralkyl, optionally substituted heteroaryl and Ar^4;

Ar^4 is selected from



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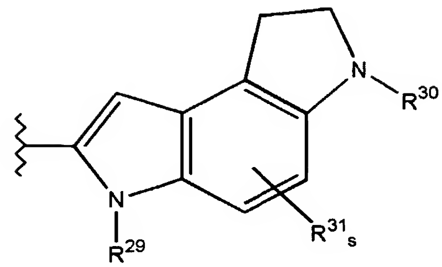

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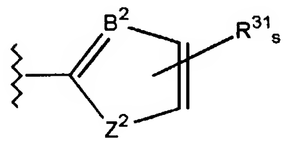
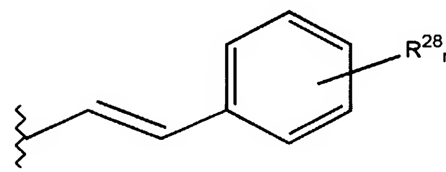


and



in which B^2 is N or CR^{32};

Z^2 is O, S, -CH=CH- or NR^{33};

the or each R^{28} is selected from C_{1-4}-alkoxy, C_{1-4}-alkyl, NO_2, CN, Cl, Br, I, $-NHR^{33}$, $-NR^{36}_2$, $-N^+R^{35}_3$-, $-NHCOR^{34}$, -COOH, $-CONHR^{35}$ and $-COOR^{35}$;

r is an integer in the range 0 to 4;

R^{29} is an amine protecting group;

R^{30} is an amine protecting group, $-CONH_2$, -COOH, $-COR^{35}$ or $-COAr^5$;

the or each R^{31} is selected from C_{1-4}-alkoxy, C_{1-4}-alkyl, NO_2, CN, Cl, Br, I, $-NHR^{33}$, $-NR^{36}_2$, $-N^+R^{36}_3$-, $NHCOR^{34}$, -COOH, $-CONHR^{35}$ and $-COOR^{35}$;

s is 0, 1 or 2;

R^{32} is selected from H, C_{1-4}-alkoxy, C_{1-4}-alkyl, NO_2, CN, Cl, Br, I, $NHCOR^{34}$, -COOH, $-CONHR^{35}$, $-NHCOOR^{35}$ and $COOR^{35}$;

the or each R^{33} is an amine protecting group;

R^{34} is selected from Ar^5, C_{1-4}-alkyl, optionally substituted phenyl, C_{7-12}-aralkyl, optionally substituted heteroaryl and ligands;

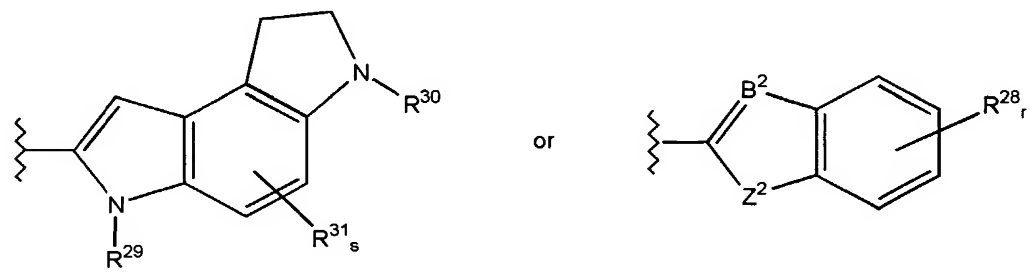
R^{35} is selected from C_{1-4}-alkyl, optionally substituted phenyl, C_{7-12}-aralkyl, optionally substituted heteroaryl and ligands;

each R^{36} is selected from C_{1-4}-alkyl, optionally substituted phenyl, C_{7-12}-aralkyl, optionally substituted heteroaryl and H

Ar^5 is selected from the same groups as Ar^4; and

Y^3 is a leaving group, provided that no more than one R^{28} or R^{31} in any one ring includes a group Ar^5.

Ar^5 is preferably



Y^3 is, for instance, selected amongst the preferred leaving groups listed above for Y. Most suitably the definition of Y^3 is Cl. Alternatively, the group Y^3 may be OH. In this case, it may be necessary to include a coupling agent to assist in the coupling reaction.

The reaction between the compound of the general formula IV or IVA and the carboxylic acid or derivative of the general formula V is carried out under conditions allowing such coupling to take place. Such conditions are similar to those generally used for formation of peptide bonds, for instance as used in peptide synthetic methods.

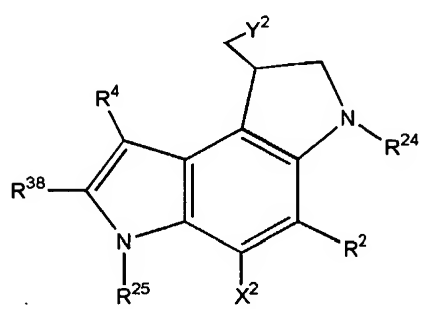
Y^2 is a hydroxy group or a leaving group, which may be the same as Y or may be converted to Y in a subsequent step.

Where, in the product, R^3 is a different group to R^{37}, the R^{37} group is subsequently derivatised to generate the desired group R^3. This is often the case where, for instance, R^3 is a group Ar^{10} or $-CONHR^9$. To produce compounds of that type the group R^{37} is, for instance, $-COOH$ or $-COOR^{10}$ and is reacted, optionally after hydrolysis/deprotection of a group $-COOR^{10}$, with an appropriate amine compound (R^9NH_2 or $Ar^{10}H$), optionally in the presence of coupling agents, to produce the amide linked compound.

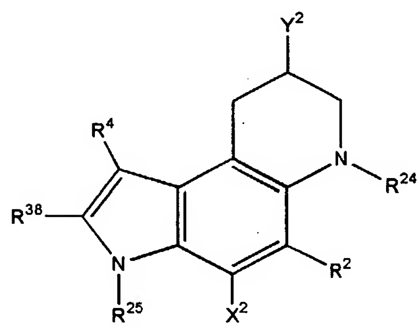
After the coupling process, it may be desirable to deprotect one or more of the protected amine groups. If further reaction, for instance with other derivatising agents such as glycosyl compounds, peptides, polymers etc is desired through any such amine groups, it may be desirable to

deprotect only those to which subsequent reaction to to take place, whilst retaining the other amine groups in a protected form. Selection of suitable amine protecting groups and protection and deprotection protocols may be made using techniques commonly utilised in peptide chemistry.

It is believed that some of the intermediates of the general formula IV or IVA may be novel compounds. According to a further aspect of the invention, there is provided a novel compound of the general formula III or IIIA



III



IIIA

in which R^2 and R^4 are as defined for formula I and IA above;

R^{38} is selected from the same groups as R^3;

X^2 is H;

Y^2 is a leaving group or a hydroxyl or protected hydroxyl group; and R^{24} and R^{25} are each H or an amine protecting group.

In compounds of the general formula III and IIIA, in the compound ready for reaction with a carboxylic acid derivative, for instance of the general formula V, R^{24} is H, whilst R^{25} should be an amine protecting group. Precursors for such compounds may have both ring nitrogen atoms in

protected form, that is in which R^{25} and R^{24} represent protecting groups. In such compounds, since it is desired for the compound to be capable of derivatisation at just one of the nitrogen atoms, preferably R^{24} and R^{25} represent different protecting groups.

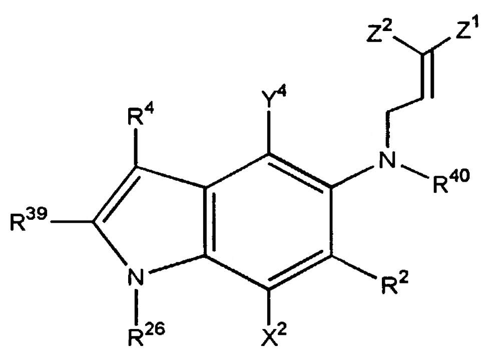
In compounds of the formula III and IIIA, the group Y^2 may be selected amongst those defined above for leaving group Y. The nature of the group Y^2 should be selected having regard to the nature of the reagent with which the compound of the formula IV or IVA, as the case may be, is to react in a subsequent step. Suitable examples of leaving group Y^2 are selected from those listed above for Y.

The compound of the formula III may be prepared in a preliminary step using as the starting material an aniline compound having a leaving group substituent Y^4 at the carbon atom ortho to the amine group substituent, and an N-substituent which is a trans 2-propen-1-yl group -$CH_2CH{=}CHY^5$, in which Y^5 is hydrogen or a group which is the same as Y^2 or may be converted to into Y^2 in a subsequent step in which the aniline derivative is reacted under cyclisation conditions, to form a dihydropyrrole ring. Preferably in the cyclisation reaction a halogen $Y^5(=Y^2)$ substituent is retained. The group Y^4 should be a radical leaving group, such as halogen, preferably I or Br. Suitable radicals for carrying out the cyclisation reaction where Y^5 is hydrogen are nitroxy compounds such as 2,2,6,6-tetramethylpiperidinyloxy (TEMPO). Where Y^5 is a radical leaving group (gY^2) the reaction may be carried out in the presence of a radical derived from azoisobutyronitrile (AIBN). In this step Y^5 does not leave. Suitable catalysts for a radical cyclisation step are tin hydride compounds such as tributyl tin hydride. This synthetic pathway is illustrated in Examples 1 and 3.

The compound of the general formula IIIA may be formed by cyclisation of an aniline compound having a radical leaving group Y^4 substituent ortho to the amine group and an N-substituent which is a 2-propen-l-yl group, preferably a trialkyl tin radical, under cyclisation conditions to form an intermediate dihydroquinonone. The cyclisation

reaction is conducted in the presence of suitable catalysts which are, for instance, palladium complexes such as tetrakis (triphenylphosphine) palladium (0), bis(triphenyl phosphine) palladium (II) chloride or palladium (II) acetate. The dihydroquinonine intermediate is oxidised to form a further intermediate which is an epoxide, for instance using a peroxide reagent. The epoxide intermediate is reduced using a suitable selective reducing agent such as a dialkyl aluminium hydride to produce the corresponding alcohol which is subsequently halogenated, for instance using carbon tetrachloride/triphenyl phosphine. This reaction is illustrated in Examples 2 and 4.

The starting compound for such reactions may be represented by the general formula VI



VI

in which R^2, R^4, R^{26}, and X^2 are the same as in the compound of the formula IV;

R^{39} is selected from the same groups as R^3;

R^{40} is an amine protecting group different from R^{26},

one of Z^1 and Z^2 is Y^5 and the other is H;

Y^5 hydrogen, or is a leaving group which is the same as or different to Y^2; and

Y^4 is a radical leaving group.

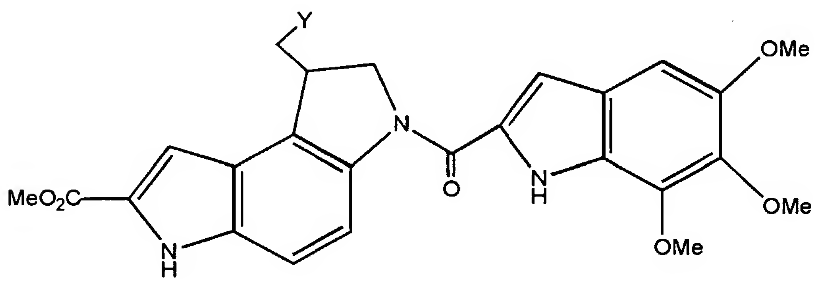
Y^4 is preferably selected from Cl, Br and I.

The compound of the general formula VI may be produced by alkylation of the sodium salt of the corresponding amiline derivative with a *cis* or *trans*-1,3-dihalo prop-2-ene compound. The *cis* starting material produces a compound of the general formula IV in which Z^2 is Y^5, the *trans*

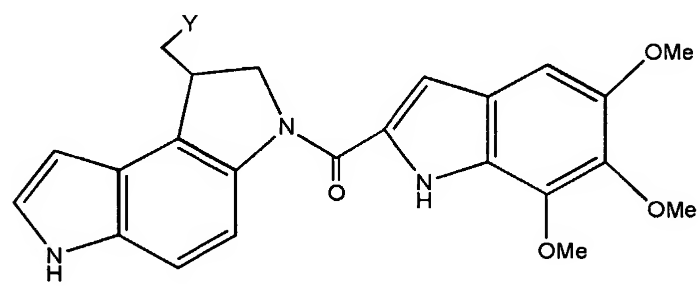
stating material a product VI in which Z^1 is Y^5. An allyl reagent produces a compound VI in which Y^5 is hydrogen,

The carboxylic acid derivative of the general formula V may be synthesised using the methods generally described in Boger *et al*, 1997 *op.cit*, for instance PDE-I and PDE-II may be synthesised using the Umezawa synthesis, the Rees-Moody synthesis, the Magnus synthesis, the Cava-Rawal synthesis, the Boger-Coleman synthesis, the Sundberg synthesis, the Martin synthesis, the Tojo synthesis. Indole-2-carboxylic acid is commercially available. Other analogues of the DNA binding sub-units of the duocarmycins, and reactive carboxylic acid derivatives thereof are described by Boger *et al*, *op.cit.* and in US-A-5843937.

Two specific examples of compounds of the general formula I and II are

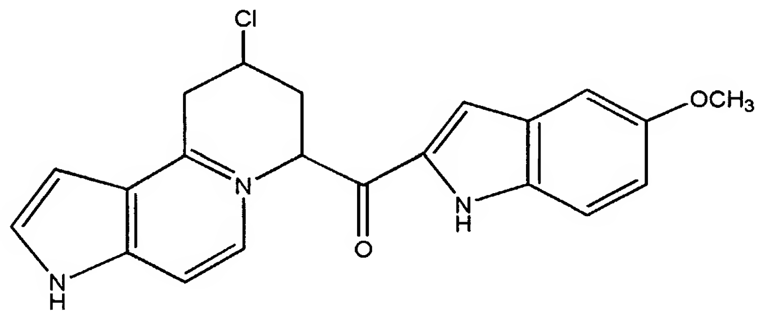


VII

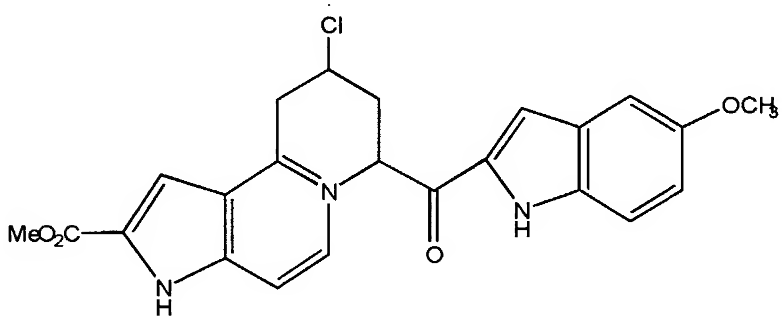


VIII

Two specific examples of a compound of the general formula IA and IIA are:



IX



X

Other examples are ethyl rather than methyl esters of compounds **VII** and X.

The present invention relates to the creation of a range of prodrugs that have little or no cytotoxic effects when in their normal state, but are highly cytotoxic (i.e. have a substantially increased cytotoxicity) when activated by oxidation or hydroxylation by CYP enzymes. This provides for a self-targeting drug delivery system in which a non cytotoxic (or negligibly cytotoxic) compound can be administered to a patient, for example in a systemic manner, the compound then being activated at the site of the tumour cells (intratumoural activation) to form a highly cytotoxic compound which acts to kill the tumour cells. The fact that the CYP isoforms are not expressed by normal cells mean that the activation of the compound only occurs at the site of the tumour cells and therefore only tumour cells are affected, thus providing a self-targeting system.

The prodrugs of the present invention have the distinct advantage of being useful in the treatment of tumours at any site in the body, meaning that even tumours that have undergone metastasis (which are normally not susceptible to site specific therapies) may be treated.

The prodrug may be an antitumour prodrug. Examples of tumours include cancers (malignant neoplasms) as well as other neoplasms e.g. innocent tumours. The prodrug may be activated by hydroxylation by isoforms of cytochrome P450's.

In a variation of the normal procedure which relies upon CYP expression within tumour cells to effect selective hydroxylation and hence activation of the prodrugs, the selectivity between tumour tissue and normal tissue can be enhanced in a two part procedure. Thus (a) infecting tumor cells with a viral vector carrying a cytochrome P450 gene and a cytochrome P450 reductase gene, wherein expression of cytochrome P450 gene and cytochrome P450 reductase gene by tumor cells enables the enzymatic conversion of a chemotherapeutic agent to its cytotoxic form within the tumor, whereby the tumor cells become selectively sensitized to the prodrug chemotherapeutic agent (b) contacting tumor cells with the prodrug chemotherapeutic agent whereby tumor cells are selectively killed.

These prodrugs are pyrrolodihydroindole (general formula I) or pyrrolo tetrahydroquinoline (general formula IA) derivatives. Their specific use as antitumour prodrugs has not been previously suggested or disclosed, nor has the suggestion that they are prodrugs having an activated hydroxylated form. Where compounds of formula (I) have been previously identified and made, they have not been identified as anti-tumour agents due to their poor (or negligible) cytotoxicity. Thus the intratumoural hydroxylation of the prodrugs of the present invention provides them with a surprising and unexpected efficacy.

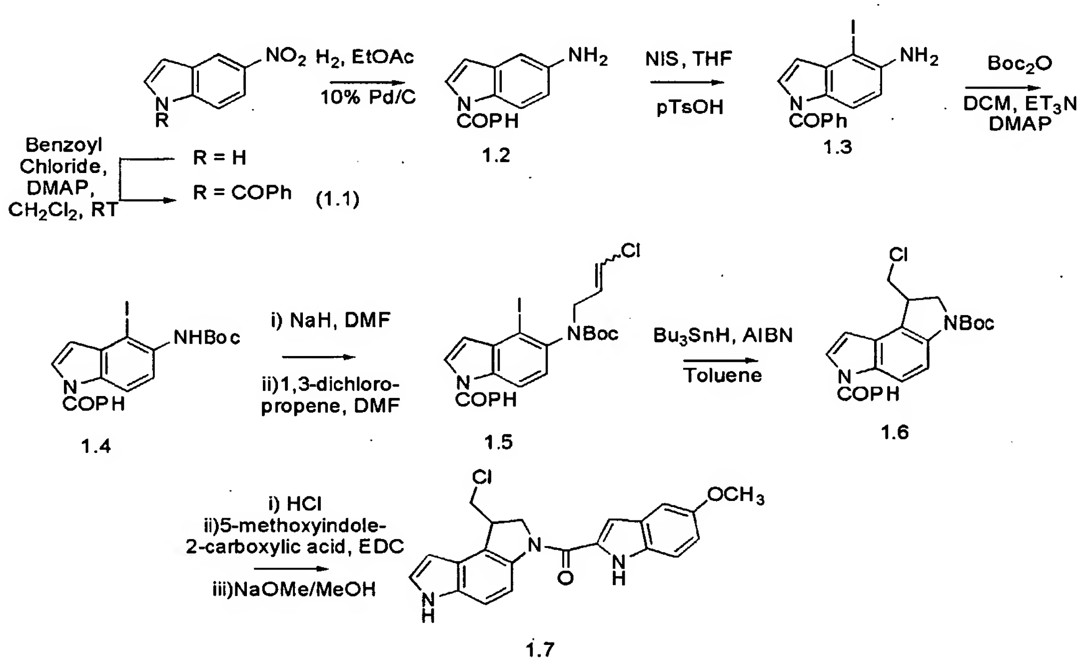
Hydroxylated forms of the prodrugs are potent DNA alkylating agents that bind in the minor groove of DNA and alkylate the purine bases at the N3 position. As such, they are potent cytotoxic agents whose exact biological mechanism of action is unknown but involves the disruption of template and

other functions of DNA. General inhibition of template function of DNA will affect and be generally cytotoxic to all dividing cells in the body and lead to unacceptable side effects in a therapeutic setting. However, the targetted production of hydroxylated forms only in tumour cells that overexpress particular isoforms of cytochrome P450's will lead to a specific cytotoxic effect only in those cells. The non-hydroxylated forms are essentially non-toxic to all cells.

The following examples illustrate the invention:

Example 1

The synthesis of one compound of the general formula I is carried out according to the following reaction scheme.



1.1 1-Benzoyl-5-nitroindole

5-nitroindole (100 mg, 0.62 mmol) in CH_2Cl_2 (1 mL) is treated with benzoyl chloride (86 mg, 0.62 mmol, 1 equiv.) and 4-dimethylaminopyridine (74 mg, 0.62 mmol, 1 equiv.). The mixture is stirred at room temperature for 1 h, diluted with CH_2Cl_2 (10 mL), washed with HCl (1M, 2 x 10 mL) and water (1 x

10 mL), dried ($MgSO_4$) and concentrated. Chromatography (Silica gel, 2 x 15 cm, 10% ethyl acetate/hexanes) gives the product.

1.2 2-Amino-1-benzoylindole

1-Benzoyl-5-nitroindole (100 mg, 0.38 mmol) in ethyl acetate (2 mL) is treated with 10% Pd/C (10 mg) and stirred under an atmosphere of hydrogen at room temperature for 4h. The resulting solution is filtered through celite and concentrated. Chromatography (Silica gel, 2 x 15 cm, 10% ethyl acetate/hexanes) gives the product.

1.3 5-Amino-1-benzoyl-4-iodoindole

5-Amino-1-benzoylindole (100 mg, 0.42 mmol) in tetrahydrofuran (THF) (1 mL) is treated with N-iodosuccinimide (103 mg, 0.46 mmol, 1.1 equiv) and 4-toluenesulfonic acid (16 mg, 0.08 mmol. 0.2 equiv.) and stirred at room temperature (RT) for 16 hours. The solution is concentrated and redissolved in ethyl acetate (10 mL). The organic layer is washed with water (1 x 10 mL), 1M HCl (2 x 10 mL) and water (1 x 10 mL), dried ($MgSO_4$) and concentrated. Chromatography (Silica gel, 2 x 15 cm, 10% ethyl acetate/hexanes) gives the product.

1.4 1-Benzoyl-5-((*tert*-butyloxy)carbonyl)amino-4-iodoindole

5-Amino-1-benzoyl-4-iodoindole (100 mg, 0.28 mmol) is stirred in CH_2Cl_2 (2 mL) and treated with di-*tert*-butyl-dicarbonate (89 mg, 0.41 mmol, 1.5 equiv), triethylamine (57 µL, 0.41 mmol, 1.5 equiv) and 4-dimethylaminopyridine (4 mg, 0.028 mmol, 0.1 equiv). After 16 h at RT, the solvents are removed under reduced pressure. Chromatography (Silica gel, 2 x 15 cm, 10% ethyl acetate/hexanes) gives the product.

1.5 1-Benzoyl-5-[N-(3-Chloro-2-propen-1-yl)-N-((*tert*-butyloxy)carbonyl)]amino-4-iodoindole

1-Benzoyl-5-(*tert*-butyloxycarbonyl)amino-4-iodoindole (100 mg, 0.22 mmol) was stirred in DMF (1 mL) and sodium hydride (26 mg, 0.66 mmol, 60% dispersion in oil, 3 equiv.) is added. After 15 min, the suspension is treated with E/Z-1,3-dichloropropene (61 µL, 0.66 mmol, 3 equiv) and the resulting solution was stirred at RT for 16 h. The solution is concentrated and water

(10 mL) is added. The aqueous solution was extracted with ethyl acetate (3 x 10 mL), the organic layers combined, dried and concentrated. The product was obtained after chromatography (Silica gel, 2 x 15 cm, 10% ethyl acetate/hexanes).

1.6 1-(Chloromethyl)-6-benzoyl-3-((*tert*-butyloxy)carbonyl)-1,2-dihydro-3H-pyrrolo[3,2-*e*]indole

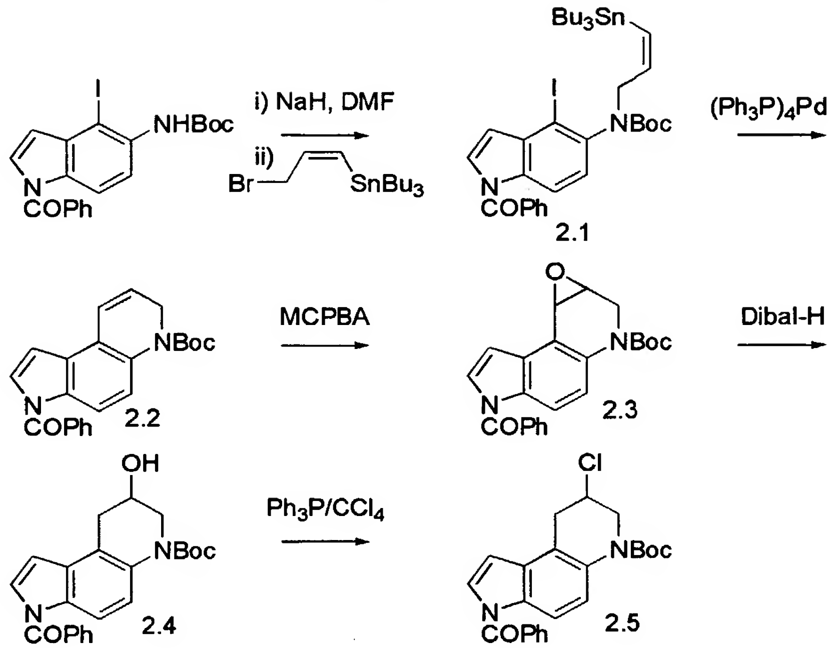
1-Benzoyl-5-[N-(3-Chloro-2-propen-l-yl)-N-((*tert*-butyloxy)carbonyl)]amino-4-iodoindole (100 mg, 0.19 mmol), poly(methylhydrosiloxane) (200 µL), bis(tributyltin) oxide (19 µL, 0.04 mmol, 0.2 equiv) and azo isobutyronitrile (AIBN) (6 mg, 0.04 mmol, 0.2 equiv) were stirred in toluene (2 mL) at 80 °C under N_2 for 4h. The solvent is then removed *in vacuo*. Chromatography (Silica gel, 2 x 15 cm, 10% ethyl acetate/hexanes) gives the product.

1.7 5-Methoxyindole extended agent. 1-(chloromethyl)-6-benzoyl-3-((5-methoxy-1H-indol-2-yl)carbonyl)-1,2-dihydro-3H-pyrrolo[3,2-e]indole

1-(Chloromethyl)-6-benzoyl-3-((*tert*-butyloxy)carbonyl)-1,2-dihydro-3H-pyrrolo[3,2-e]indole (100 mg, 0.24 mmol) is treated with a solution of hydrochloric acid in ethyl acetate (4M, 500 µL). After 30 min, the solvent is concentrated and dimethyl formamide (DMF) (1 mL) is added. The solution is treated with 1-[(3-dimethylamino)propyl]-3-ethyl carbodimide (EDC) (140 mg, 0.73 mmol) and 5-methoxyindole-2-carboxylic acid (140 mg, 0.73 mmol). After 16 h, the solvent is removed under reduced pressure. Chromatography (Silica gel, 2 x 15 cm, 10% ethyl acetate/hexanes) gives the product. The 6-benzoyl protecting group may be removed by sodium methoxide in methanol, followed by removal of the solvent.

<u>Example 2</u>

The following example illustrates the synthesis of a compound of the general formula 1A in which R^1 is OR^8 and R^8 is tBu. It is suitable for extending by a step analogous to step 1.7 above, to form a further compound of the formula IA in which R^1 is Ar, and optionally subsequently deprotected at the nitrogen atom of the indole ring.



2.1 1-Benzoyl-5-[N-(3-(tributylstannyl)-2-propen-1-yl)-N-((*tert*-butyloxy)carbonyl)]amino-4-iodoindole

1-benzoyl-5-(*tert*-butyloxycarbonyl)amino-4-iodoindole (100 mg, 0.22 mmol) is stirred in DMF (1 mL) and sodium hydride (26 mg, 0.66 mmol, 60% dispersion in oil, 3 equiv.) is added. After 15 min, the suspension is treated with E/Z-1-tributylstannyl-3-bromopropene (270 mg, 0.66 mmol, 3 equiv) (Boger, D. L.; McKie, J. A.; Boyce, C. W. *Synlett* 1997, 515-516) and the resulting solution is stirred at RT for 16 h. The solution was concentrated and water (10 mL) is added. The aqueous solution is extracted with ethyl acetate (3 x 10 mL), the organic layers combined, dried and concentrated. The product was obtained after chromatography (Silica gel, 2 15 cm, 10% ethyl acetate/hexanes)

2.2 1,2-Dihydro-1-((*tert*-butyloxy)carbonyl)-5,6-(9-benzoylpyrrolo)quinoline.

1-Benzoyl-5-[N-(3-(tributylstannyl)-2-propen-1-yl)-N-((*tert*-butyloxy)carbonyl)]amino-4-iodoindole (100 mg, 0.12 mmol) and tetrakis(triphenylphosphine)palladium(0) (32 mg, 0.2 equiv) are stirred in toluene (2 mL) at 50°C under N_2 for 2 h. The solvent is then removed *in*

vacuo. Chromatography (Silica gel, 2 x 15 cm, 10% ethyl acetate/hexanes) gives the product.

2.3 3,4-Epoxy-1-((*tert*-butyloxy)carbonyl)-1,2,3,4-tetrahydro-5,6-(9-benzoylpyrrolo)quinoline.

1,2-dihydro-1-((*tert*-butyloxy)carbonyl)-5,6-(9-benzoylpyrrolo)quinoline. (100 mg, 0.27 mmol) and 3-chloroperoxy benzoic acid (68 mg, 0.40 mmol, 1.5 equiv) were stirred in CH_2Cl_2 (2 mL) at –78 °C to –30 °C under N_2 for 2 h. The solvent is then removed *in vacuo*. Chromatography (Silica gel, 2 x 15 cm, 10% ethyl acetate/hexanes) gives the product.

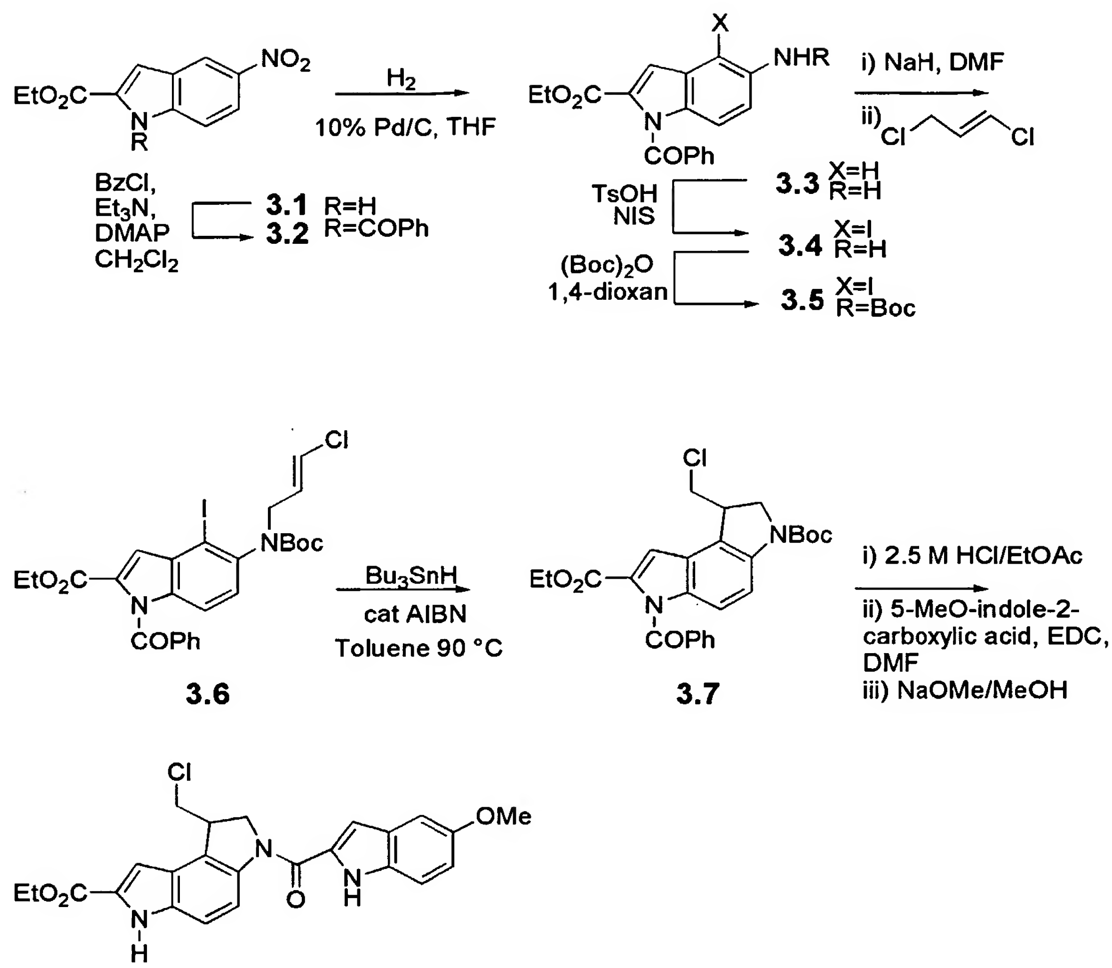
2.4 4-Hydroxy-1-((*tert*-butyloxy)carbonyl)-1,2,3,4-tetrahydro-5,6-(9-benzoyl)pyrroloquinoline.

3,4-epoxy-1-((*tert*-butyloxy)carbonyl)-1,2,3,4-tetrahydro-5,6-(9-benzoylpyrrolo)quinoline (100 mg, 0.26 mmol) was treated with disobutyl aluminium hydride (Dibal-H) (55 mg, 0.39 mmol, 1.5 equiv) in THF (2 mL),at –78 °C to –30 °C under N_2. After 1 h, the reaction is quenched by the addition of water (2 mL) and the resulting solution is extracted with ethyl acetate (3 x 10 mL), the organic layers combined, dried and concentrated. The solvent is removed *in vacuo*. Chromatography (Silica gel, 2 x 15 cm, 10% ethyl acetate/hexanes) gives the product.

2.5 4-Chloro-1-((*tert*-butyloxy)carbonyl)-1,2,3,4-tetrahydro-5,6-(9-benzoyl)pyrroloquinoline

4-hydroxy-1-((*tert*-butyloxy)carbonyl)-1,2,3,4-tetrahydro-5,6-(9-benzoyl)pyrroloquinoline (100 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) is treated with a prepared solution of PPh_3 (137 mg, 0.52 mmol, 2 equiv) and CCl_4 (200 mL) in CH_2Cl_2 (2 mL) at RT. After 4 h, the solvent is removed *in vacuo*. Chromatography (Silica gel, 2 x 15 cm, 10% ethyl acetate/hexanes) gives the product.

Example 3



3.8

3.1 Ethyl 1-benzoyl-5-nitroindole-2-carboxylate (3.2)

Ethyl 5-nitroindole-2-carboxylate (3.1) (1.5 g, 6.41 mmol) in CH_2Cl_2 (30ml) was treated with benzoyl chloride (1.19 ml, 10.26 mmol), Et_3N (891 μl, 6.41 mmol) and DMAP (783 mg, 6.41 mmol). The mixture was stirred for 16 h. 10% $NaHCO_3$ (10 ml) and CH_2Cl_2 (10 ml) were added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with H_2O (10 ml), 5 % HCl (10 ml) and H_2O (10 ml). The solution was dried ($MgSO_4$) and concentrated. The residue was crystalised from EtOAc/Hex 1:9 to afford 1.85g (87 %) of **3.2** as a yellow powder: ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm 8.66 (d, 1 H), 8.25 (d, 1

H), 7.80 (d, 1 H), 7.6-7.72 (m, 3H), 7.48 (m, 3 H), 4.00 (q, 2 H), 1.10 (t, 3 H). FABMS (NBA/NaI) m/z 339 (M + H^+ expected 339)

3.2 Ethyl 5-amino-1-benzoylindole-2-carboxylate (3.3).

A solution of 3.2 (1.86 g, 5.5 mmol) and 10% Pd/C (440 mg) in dry THF (30 ml) was stirred under H_2 for 16 hrs. The resulting mixture was filtered through celite which was washed with EtOAc (40ml) and the filtrate was concentrated. The residue was purified by chromatography (SiO_2, 0 to 40 % EtOAc in hexanes) to afford 3.3 (1.63g, 96 %) as a bright yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm 7.40 – 7.72 (m, 6 H), 7.18 (s, 1 H), 6.92 (d, 1 H), 6.82 (dd, 1 H), 3.92 (q, 2 H), 3.68 (br s, 2 H), 1.06 (t, 3 H); FABMS: (NBA/NaI) m/z 308 (M + H^+ expected 308).

3.3 Ethyl 5-amino-1-benzoyl-4-iodoindole-2-carboxylate (3.4)

5-amino-1-benzoylindole (1.63 g, 5.29 mmol) in THF (75 mL) was treated with N-iodosuccinimide (1.89 g, 8.46 mmol) and 4-toluenesulfonic acid (364 mg, 2.12 mmol) and stirred at RT for 16 hours. The solution was concentrated and redissolved in ethyl acetate (100 mL). The organic layer was washed with water (1 x 100 mL), 1M HCl (2 x 100 mL) and water (1 x 100 mL), dried ($MgSO_4$) and concentrated. Chromatography (SiO_2, 10% ethyl acetate/hexanes) gave the product (1.17g, 51 %) as a bright yellow solid. ^{1}H NMR (250MHz, $CDCl_3$) δ ppm 7.30-7.70 (m, 6 H), 7.30 (s, 1 H), 6.80 (d, 1 H), 4.05 (s, 2 H), 3.85 (q, 2 H), 1.0 (t, 3H) FABMS (NBA/NaI) m/z 434 (M + H^+ expected 434),457 (M + Na^+ expected 457).

3.4 Ethyl 1-benzoyl-5-(*N*-(*tert*-butyloxycarbonyl) -4-iodoindole-2-carboxylate (3.5)

A mixture of **3.4** (1.17 g, 2.70 mmol), $(Boc)_2O$ (9.40 g, 43 mmol) and Et_3N (375 μL, 2.70 mmol) in dioxan (100 mL) was heated to 100 °C under N_2 for 48 h. Upon completion, the solution was cooled, concentrated and purified by flash chromatography (SiO_2, 0-20% EtOAc in hexane) to afford **3.5** (1.3g, 90 %) as a yellow oil. FABMS (NBA.NaI) 535 (M + H^+ expected 535).

3.5 Ethyl 1-benzoyl-5-[*N*-(3-chloro-2-propen-1-yl)-*N*-((*tert*-butyloxy)carbonyl)]amino-4-iodoindole (3.6)

1-benzoyl-5-(*tert*-butyloxycarbonyl)amino-4-iodoindole (100 mg, 0.22 mmol) was stirred in DMF (1 mL) and sodium hydride (26 mg, 0.66 mmol, 60% dispersion in oil, 3 equiv.) was added. After 15 min, the suspension was treated with E/Z-1,3-dichloropropene (61 μL, 0.66 mmol, 3 equiv) and the resulting solution was stirred at RT for 16 h. The solution was concentrated and water (10 mL) was added. The aqueous solution was extracted with ethyl acetate (3 ′ 10 mL), the organic layers combined, dried and concentrated. The (3.6) product was obtained after chromatography (SiO_2, 10% ethyl acetate/hexanes) as a yellow oil (125 mg, 94 %). FABMS (NBA/NaI) m/z 609 (M + H^+ expected 609).

3.6 Ethyl 6-benzoyl-1-(chloromethyl)-3-((*tert*-butyloxy)carbonyl)-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate (3.7)

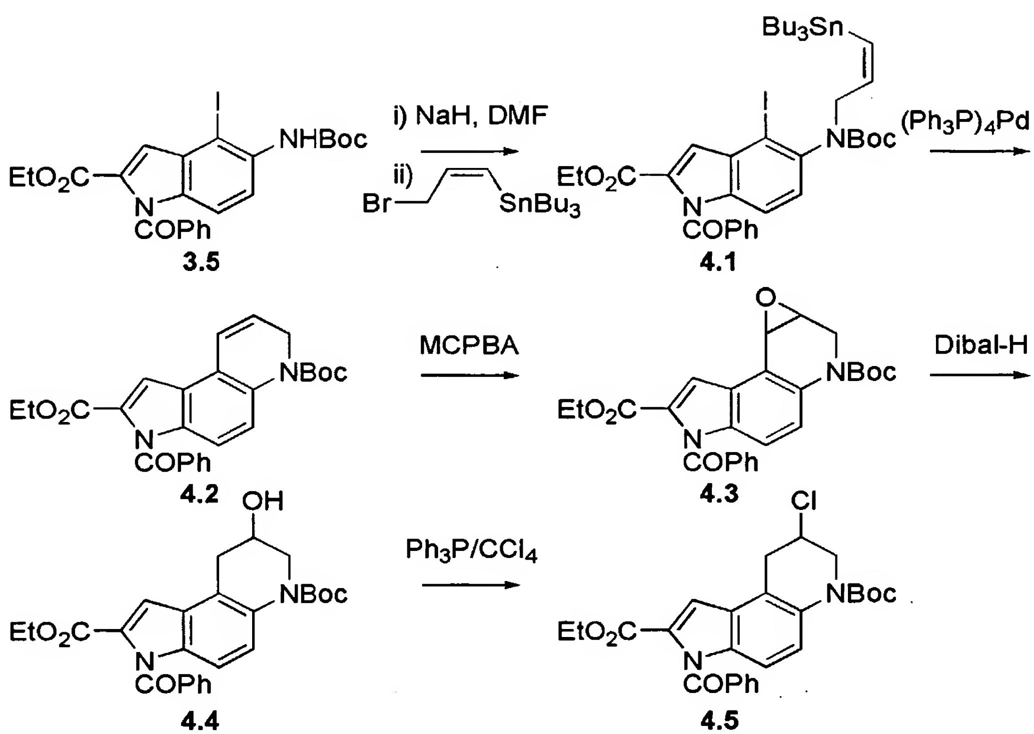
Compound **3.6** (100 mg, 0.19 mmol), and AIBN (6 mg, 0.04 mmol, 0.2 equiv) were stirred in toluene (2 mL) at 80°C under N_2. Bu_3SnH (51 μL, 0.19 mmol) was added in 4 portions over 1 h.. The solvent was then removed *in vacuo*. Chromatography (SiO_2 10% ethyl acetate/hexanes) gave the product (3.9) (72 mg, 78 %) as an oil. FABMS (NaI/NBA) m/z 483 (M + H^+ expected 483).

3.7 Ethyl 1-(chloromethyl)-3-((5-methoxy-1*H*-indol-2-yl)carbonyl)-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate (3.8)

Compound **3.7**(100 mg, 0.21 mmol) was treated with a solution of hydrochloric acid in ethyl acetate (4M, 500 μL). After 30 min, the solvent was concentrated and DMF (1 mL) was added. The solution was treated with EDC (120 mg, 0.63mmol) and 5-methoxyindole-2-carboxylic acid (120 mg, 0.63 mmol). After 16 h, the solvent was removed under reduced pressure and the residue (the 6N-benzoyl protected precursor of compound 3.8) was dissolved in CH_3OH (1 mL). A solution of $NaOCH_3$ in CH_3OH (2M, 100 μL) was then added and the solution stirred for 10 minutes. The solvent was removed and chromatography (SiO_2, 10% ethyl acetate/hexanes) gave the product (3.8) (100 mg, 86 %). FABMS (NBA/NaI) m/z 557 (M + H^+ expected

557).

Example 4



4.1 Ethyl 1-Benzoyl-5-[N-(3-(tributylstannyl)-2-propen-1-yl)-N-((*tert*-butyloxy)carbonyl)]amino-4-iodoindole-7-carboxylate (4.1)

Ethyl 1-benzoyl-5-(*tert*-butyloxycarbonyl)amino-4-iodoindole (3.5, synthesised as described in Example 3.1-3.4) (100 mg, 0.18 mmol) was stirred in DMF (1 mL) and sodium hydride (21 mg, 0.54 mmol, 60% dispersion in oil, 3 equiv.) was added. After 15 min, the suspension was treated with E/Z-1-tributylstannyl-3-bromopropene (221 mg, 0.54 mmol, 3 equiv) and the resulting solution was stirred at RT for 16 h. The solution was concentrated and water (10 mL) was added. The aqueous solution was extracted with ethyl acetate (3 x 10 mL), the organic layers combined, dried and concentrated. The product was obtained after chromatography (SiO_2, 10% ethyl acetate/hexanes) as a colourless solid (132 mg, 92 %). FABMS (NBA/NaI) m/z 792 (M + H^+ expected 792).

4.2 5,6-(9-Benzoyl-8-(ethyloxy)carbonylpyrrolo)-1-((*tert*-butyloxy)carbonyl)- 2,4-dihydroquinoline (4.2)

Compound **4.1** (100 mg, 0.12 mmol) and tetrakis(triphenylphosphine)palladium(0) (32 mg, 0.2 equiv) were stirred in toluene (2 mL) at 50°C under N_2 for 2 h. The solvent was then removed *in vacuo*. Chromatography (SiO_2, 10% ethyl acetate/hexanes) gave the product (50mg, 94 %) as a yellow oil. FABMS (NBA/NaI) m/z 447 ($M + H^+$ expected 447).

4.3 5,6-(9-benzoyl-8-(ethyloxy)carbonylpyrrolo)-1-((*tert*-butyloxy)carbonyl)-3,4-epoxy--1,2,3,4-tetrahydroquinoline (4.3)

Compound **4.2** (100 mg, 0.22 mmol) and MCPBA (57 mg, 0.33 mmol, 1.5 equiv) were stirred in CH_2Cl_2 (2 mL) at –30 °C under N_2 for 2 h. The solvent was then removed *in vacuo*. Chromatography (SiO_2, 10% ethyl acetate/hexanes) gave the product (70 mg, 69%) as an oil. FABMS (NBA/NaI) m/z 463 ($M + H^+$ expected 463).

4.4 5,6-(9-benzoyl-8-(ethyloxy)carbonylpyrrolo)-1-((*tert*-butyloxy)carbonyl)-4-hydroxy-1,2,3,4-tetrahydroquinoline (4.4)

Compound **4.3** (100 mg, 0.22 mmol) was treated with Dibal-H (46 mg, 0.33 mmol, 1.5 equiv) in THF (2 mL), at –30 °C under N_2. After 1 h, the reaction was quenched by the addition of water (2 mL) and the resulting solution was extracted with ethyl acetate (3 x 10 mL), the organic layers combined, dried and concentrated. The solvent was removed *in vacuo*. Chromatography (SiO_2, 10% ethyl acetate/hexanes) gave the alcohol (85 mg, 83 %). FABMS (NBA/NaI) m/z 465 ($M + H^+$ expected 465).

4.5 5,6-(9-benzoyl-8-(ethyloxy)carbonylpyrrolo)-1-((*tert*-butyloxy)carbonyl)-4-chloro-1,2,3,4-tetrahydroquinoline (4.5)

Compound **4.4** (100 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) was treated with a prepared solution of PPh_3 (116 mg, 0.44 mmol, 2 equiv) and CCl_4 (200 μL) in CH_2Cl_2 (2 mL) at RT. After 24 h, the solvent was removed *in vacuo*. Chromatography (SiO_2, 10% ethyl acetate/hexanes) gave the target compound as an oil (95 mg, 90 %). FABMS (NBA/NaI) m/z 484 ($M + H^+$

expected 484). The compound may be deprotected by removal of the tBOC group, a DNA-binding sub-unit conjugated to the nitrogen atom of the tCtra hydroquinoline ring and the indole nitrogen subsequently deprotected by steps analogous to those of Example 3.7.

Example 5 Biological testing of Ethyl 1-(chloromethyl)-3-((5-methoxy-1*H*-indol-2-yl)carbonyl)-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate (3.8)

Materials and Methods

5.1 Incubation mixtures of compound and microsomes

Test compound (synthesised in example 3) activation by CYP enzymes was carried out using NADPH supplemented rat liver microsomes. Incubation mixtures comprised microsomal protein (1 mg/ml), reduced-nicotinamide adenine dinucleotide phosphate (NADPH,10mM) and phosphate buffer (pH7.4, 100mM). Test compound (0.01 – 100 μM final concentration) in DMSO (20μl) was added to the microsomal incubation mixtures (0.5ml) and incubated for 60 min at 37C. Control incubates contained test compound and microsomal incubation mixture terminated at 0 time. All incubations were terminated by addition of an equal volume of ice-cold acetonitrile and microfuged for 3 min. Aliquots of the supernatant were added to cells in culture.

5.2 Cell culture based cytotoxicity measurement

Chinese Hamster Ovary (CHO) cell were grown in MEM supplemented with 10% dialysed FBS and G418 (400μg/ml). All cells were seeded at an initial density of 1000 cells/well in 96-well-plates, incubation at 37°C for 24 hours. Aliquots (0.1ml) of the test compound/microsomal/acetonitrile supernatnant was then added to the CHO cells. Cells were then incubated for 24 hours at 37°C, 5% CO_2. After this time period MTT (50 μl; 2mg/ml stock solution) was added to each well and cells were incubated for a further 4 hours. During this time period MTT, a hydrogen acceptor tetrazolium salt, is reduced to formazan dye by mitochondrial dehydrogenase of viable cells. The media

was aspirated from cells and DMSO (100 µl/well) added to solubilise the coloured formazan dye. Absorbance of the formazan dye in the 96-well-plates was then determined at 550nm. The effect of microsomal activation by the test compound on the arrest of CHO cell growth could be determined by comparing the IC_{50} (concentration that inhibited cell growth by 50%) with and without microsomal incubation.

Results

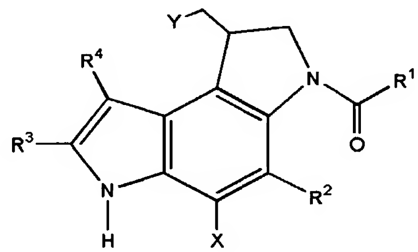
compound	CHO IC50 (µM)		AF
	+activation	-activation	
3.8	0.06±0.02	4.3±0.41	71.7*

Effect of compound **3.8** and its metabolism (activation) product on the survival of Chinese hamster ovary cells in culture. Cells were incubated for 24 hours with supernatants from reaction mixtures of compound **3.8** with NADPH fortified rat liver microsomes. IC_{50} represents the concentration of drug required to inhibit cell growth by 50%. Values are expressed as the mean ± sd for three experiments. See methods for full details of metabolism. AF = activity factor i.e. the ratio of IC_{50} cytotoxicity values obtained for ± compound **3.8** activation.

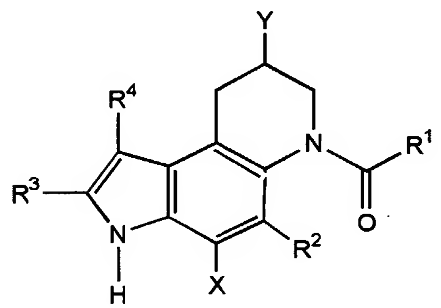
* represents significance at p>0.05.

CLAIMS

1. Use of a compound of the general formula I or IA or a salt thereof in the manufacture of a composition for use in a method of treatment by therapy of an animal:



I



IA

in which X is H;

Y is a leaving group

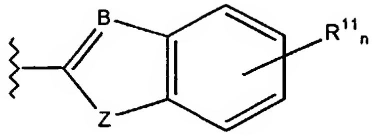
R^1 is -Ar, NH_2, R^8 or $-OR^8$;

R^2 and R^4 are each independently selected from H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, -CN, Cl, Br, I, $-NO_2$, $-NH_2$, $-NHCOR^9$, -COOH, $-CONHR^9$, $-NHCOOR^9$, $-COOR^9$ and $COAr^{10}$;

R^3 is selected from H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, -CN, Cl, Br, I, $-NO_2$, $-NH_2$, $-NHCOR^9$, -COOH, $-CONHR^9$, $-NHCOOR^9$ and $-COOR^9$;

R^8 and R^9 are independently selected from C_{1-4} alkyl, optionally substituted phenyl, C_{7-12}-aralkyl and optionally substituted heteroaryl and ligands;

Ar is selected from



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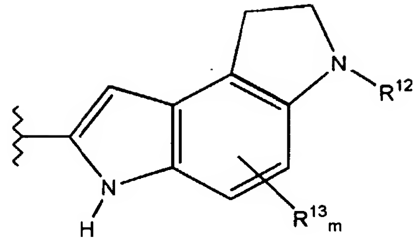

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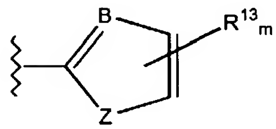

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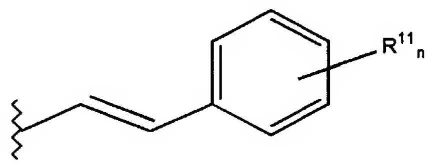


in which B is N or CR^{14};

Z is O, S -CH=CH- or NH;

the or each R^{11} is selected from -OH, C_{1-4} alkoxy, C_{1-4} alkyl, $-NO_2$, -NH_2, $-NHR^{10}$, $-NR^{10}_2$, $-N^+R^{10}_3$, -CN, Cl, Br, I, $-NHCOR^{15}$, -COOH, $-CONHR^{16}$, -$NHCOOR^{16}$ and $COOR^{16}$;

n is an integer in the range 0 to 4;

the or each of R^{10} is selected from C_{1-4}alkyl, optionally substituted phenyl, C_{7-12}-aralkyl optionally substituted heteroaryl

R^{12} is H, $-COAr^1$, $-CONH_2$, -COOH, $-COR^{16}$ or $-COOR^{16}$;

the or each R^{13} is selected from OH, C_{1-4} alkoxy, C_{1-4} alkyl, $-NO_2$, -NH_2, $-NHR^{10}$, $-NR^{10}_2$, $-N^+R^{10}_3$, -CN, Cl, Br, I, $-NHCOR^{15}$, -COOH, $-CONHR^{16}$, -$NHCOOR^{16}$ and $-COOR^{16}$;

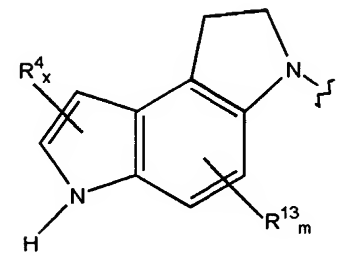
m is 0, 1 or 2;

R^{14} is selected from OH, C_{1-4} alkoxy, C_{1-4} alkyl, $-NO_2$, $-NH_2$, -CN, Cl, Br, I, $-NHCOR^{15}$, -COOH, $-CONHR^{16}$, $-NHCOOR^{16}$, $-COOR^{16}$ and H;

R^{15} is selected from C_{1-4} alkyl, optionally substituted phenyl, optionally substituted heteroaryl, C_{7-12} aralkyl Ar^1 and a ligand;

R^{16} is selected from C_{1-4}alkyl, optionally substituted phenyl, C_{7-12}-aralkyl, optionally substituted heteroaryl and a ligand; and

Ar^{10} is



in which x is 0, 1 or 2;

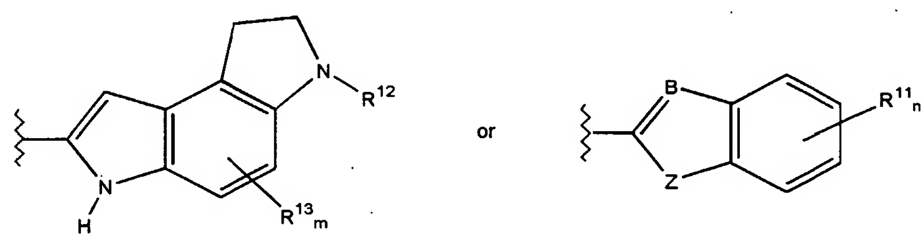
Ar^1 is selected from the same groups as Ar provided that no more than one group R^{11} or R^{13} in any one ring includes a group Ar^1.

2. Use according to claim 1 in which the animal is a human.

3. Use according to claim 1 or claim 2 in which the treatment is of a tumour.

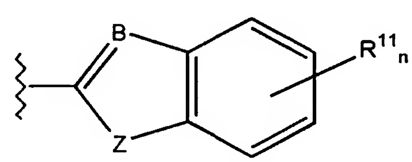
4. Use according to any preceding claim in which Y is selected from $-OCOOR^5$, $-OCONHR^6$, Cl, Br, and $-OSOOR^7$, in which R^5, R^6 and R^7 are independently selected from C_{1-4} alkyl, optionally substituted phenyl, C_{7-12}-aralkyl and optionally substituted heteroaryl; preferably Cl.

5. Use according to any preceding claim in which Ar^1 is



6. Use according to any preceding claim in which R^1 is Ar.

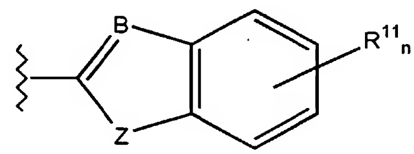
7. Use according to claim 6 in which Ar is a group



8. Use according to claim 7 in which n is at least one and one of

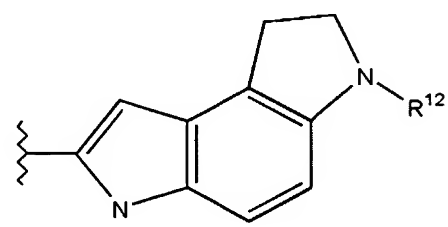
the groups R^{11} of the Ar group is -NHCOAr^1.

9. Use according to claim 8 in which Ar^1 is a group



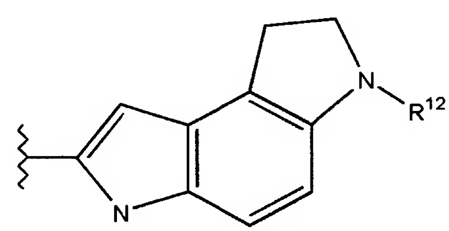
10. Use according to claim 9 in which, in Ar^1, n is at least 2 and R^{11} is other than -NHCOAr^1, or n is 0.

11. Use according to claim 6 in which Ar is a group



12. Use according to claim 11 in which R^{12} is -COAr^1.

13. Use according to claim 12 in which Ar^1 is a group



14. Use according to claim 13 in which, in Ar^1, R^{12} is other than -COAr^1.

15. Use according to any preceding claim in which R^2 is H.

16. Use according to any preceding claim in which R^3 is H or COOMe.

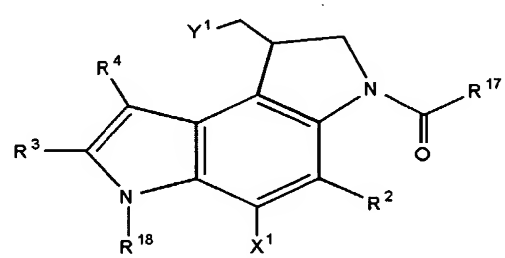
17. Use according to any preceding claim in which R^4 is H.

18. A compound of the general formula I as defined in any of claims 1 and 4 to 17 for use in the treatment an animal by therapy.

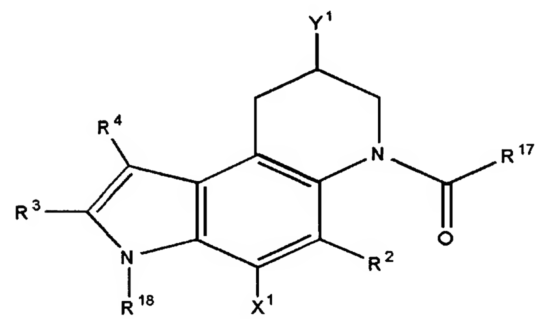
19. A pharmaceutical composition comprising a compound of the

general formula I as defined in any of claims 1 and 4 to 17 and a pharmaceutically acceptable excipient.

20. A compound of the general formula II or IIA or a salt thereof



II



IIA

in which R^2, R^3 and R^4 are as defined in claim 1

X^1 is H;

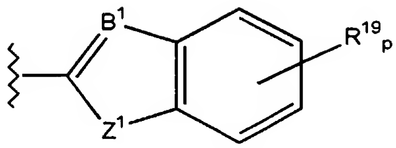
Y^1 is a leaving group;

R^{18} is H or an amine protecting group;

R^{17} is R^8, $-OR^8$, NH_2 or Ar^2;

R^8 is as defined in claim 1;

Ar^2 is selected from



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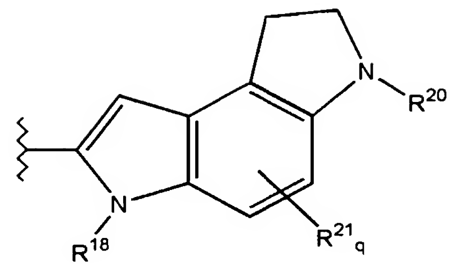

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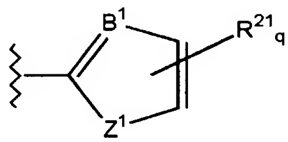

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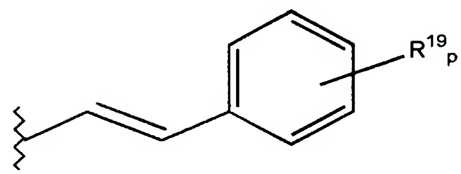


in which B^1 is N or CR^{40};

R^{40} is selected from H, OH, C_{1-4}-alkoxy, C_{1-4}-alkyl, $-NO_2$, $-NH_2$, -CN, Cl, Br, I, $-NHCOR^{22}$, -COOH, $-CONHR^{23}$, $-NHCOOR^{23}$ and $-COOR^{23}$;

Z^1 is O, S, -CH=CH- or NR^{18};

the or each R^{19} is selected from OH, C_{1-4} alkoxy C_{1-4} alkyl, NO_2, $-NHR^{18}$, $-NHR^{23}$, $-NR^{23}_2$, $-N^+R^{23}_3$, -CN, Cl, Br, I, $-NHCOR^{22}$, -COOH, -$CONHR^{23}$ and $-COOR^{23}$;

p is an integer in the range 0 to 4;

R^{20} is H, $COAr^3$, $-CONH_2$, -COOH $-COR^{23}$ or $-COOR^{23}$;

the or each R^{21} is selected from OH, C_{1-4} alkoxy C_{1-4} alkyl, NO_2, $-NHR^{18}$, $-NHR^{23}$, $-NR^{23}_2$, $-N^+R^{23}_3$, -CN, Cl, Br, I, $-NHCOR^{22}$, -COOH, -$CONHR^{23}$ and $-COOR^{23}$;

q is 0, 1 or 2;

R^{22} is selected from C_{1-4} alkyl, optionally substituted phenyl, optionally substituted heteroalkyl, C_{7-12} aralkyl, Ar^3 and ligands;

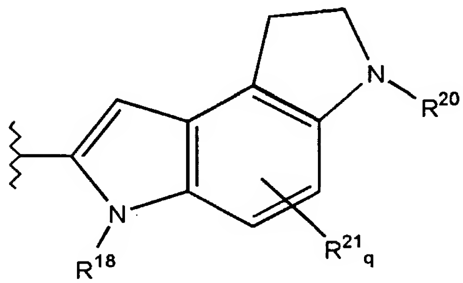
R^{23} is selected from C_{1-4}alkyl, optionally substituted phenyl, C_{7-12}-aralkyl and optionally substituted heteroaryl and a ligand; and

Ar^3 is selected from the same groups as Ar^2 provided that no more than one R^{19} or R^{21} in any one ring includes a group Ar^3.

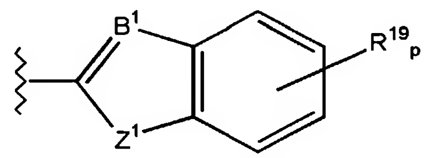
21. A compound according to claim 20 in which the or each R^{18} is H.

22. A compound according to claim 20 or claim 21 in which Y^1 is selected from $-OCOOR^5$, $-OCONHR^6$, Cl, Br, I, -OTos, or $-OSOOR^7$ in which R^5, R^6 and R^7 are as defined in claim 4, preferably Cl.

23. A compound according to any of claims 20 to 22 in which Ar^3 is

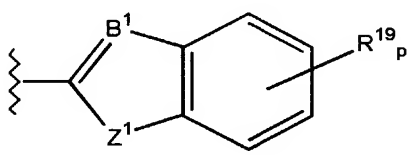


or



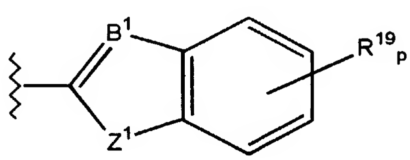
24. A compound according to any of claims 20 to 23 in which R^{17} is Ar^2.

25. A compound according to claim 24 in which Ar^2 is a group



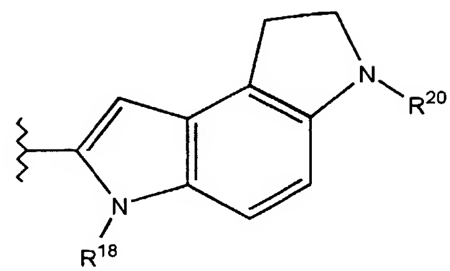
26. A compound according to claim 25 in which p is at least 1 and one of the groups R^{19} of the group R^{17} is a group $-NHCOAr^3$.

27. A compound according to claim 26 in which Ar^3 is



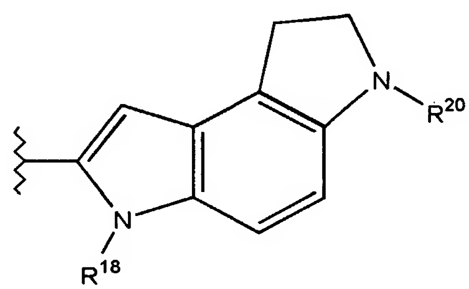
28. A compound according to claim 27 in which, in Ar^3, p is at least 1 and R^{19} is other than $-NHCOAr^3$, or p is 0.

29. A compound according to claim 24 in which Ar^2 is a group



30. A compound according to claim 29 in which R^{20} is $COAr^3$.

31. A compound according to claim 30 in which Ar^3 is



32. A compound according to claim 31 in which, in Ar^3, R^{20} is other than $-COAr^3$.

33. A compound according to any of claims 20 to 32 in which R^2 is H.

34. A compound according to any of claims 20 to 33 in which R^3 is H COOMe.

35. A compound according to any of claims 20 to 34 in which R^4 is H.

36. A compound according to claim 20 selected from:-

1-(chloromethyl)-6-benzoyl-3-((*tert*-butyloxy)carbonyl)-1,2-dihydro-3H-pyrrolo[3,2-*e*]indole;

1-(chloromethyl)-6-benzoyl-3-((5-methoxy-1H-indol-2-yl)carbonyl)-1,2-dihydro-3H-pyrrolo[3,2-e]indole;

1-(chloromethyl)-3-((5-methoxy-1H-indol-2-yl)carbonyl)-1,2-dihydro-3H-pyrrolo[3,2-e]indole;

4-chloro-1-((*tert*-butyloxy)carbonyl)-1,2,3,4-tetrahydro-5,6-(9-

benzoyl)pyrroloquinoline;

4-chloro-1-(5-methoxy-1H-indol-2-ylcarbonyl)-1,2,3,4-tetrahydro-5,6-(9-benzoyl)pyrroloquinoline;

4-chloro-1-(5-methoxy-1H-indol-2-ylcarbonyl)-1,2,3,4-tetrahydro-5,6)pyrroloquinoline;

ethyl 6-benzoyl-1-(chloromethyl)-3-((*tert*-butyloxy)carbonyl)-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate;

ethyl 6-benzoyl-1-(chloromethyl)-3-((5-methoxy-1*H*-indol-2-yl)carbonyl)-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate;

ethyl 1-(chloromethyl)-3-((5-methoxy-1*H*-indol-2-yl)carbonyl)-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate;

5,6-(9-benzoyl-8-(ethyloxy)carbonylpyrrolo)-1-((*tert*-butyloxy)carbonyl)-4-chloro-1,2,3,4-tetrahydroquinoline;

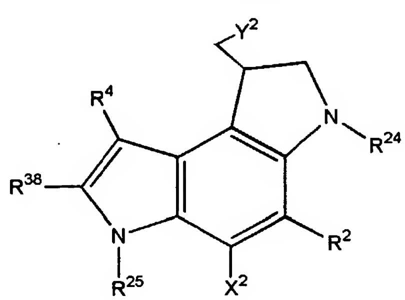
5,6-(9-benzoyl-8-(ethyloxy)carbonylpyrrolo)-1-(5-methoxy-1H-indol-2-ylcarbonyl)-4-chloro-1,2,3,4-tetrahydroquinoline; and

5,6(8-(ethyloxy)carbonylpyrrolo)-1-(5-methoxy-1H-indol-2-ylcarbonyl)-4-chloro-1,2,3,4-tetrahydroquinoline.

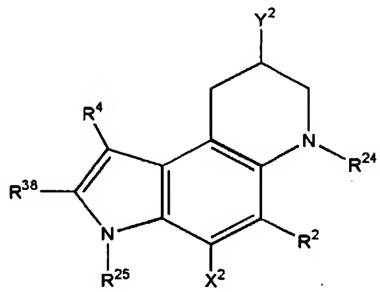
37. A compound according to any of claims 20 to 36 for use in the treatment of an animal by therapy.

38. A pharmaceutical composition comprising a compound according to any claims 20 to 36 and a pharmaceutically acceptable excipient.

39. A compound of the general formula III or IIIA



III



IIIA

in which R^2 and R^4 are as defined in claim 1;

R^{38} is selected from the same groups as R^3 defined in claim 1;

X^2 is H;

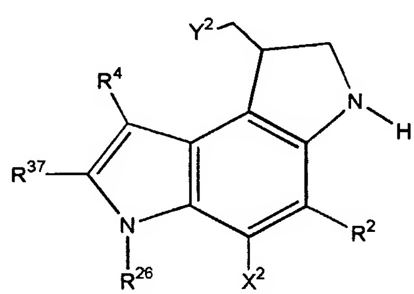
Y^2 is a leaving group or a hydroxyl or a protected hydroxyl group and R^{24} and R^{25} are each H or an amine protecting group.

40. A compound according to claim 39 in which R^{24} and R^{25} are different from one another.

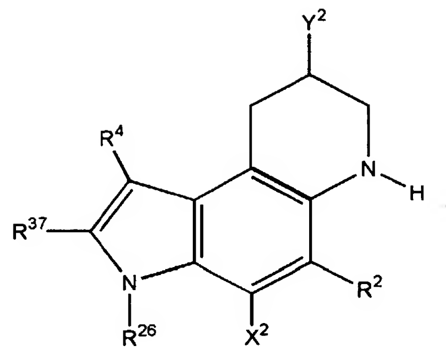
41. A compound according to claim 40 in which R^4 is BOC and R^{25} is -COPh.

42. A compound according to any of claims 39 to 41 in which Y^2 is selected from -OCOOR^5, -OCONHR^6, Cl, Br, and -OSOOR^7, in which R^5, R^6 and R^7 are independently selected from C_{1-4} alkyl, optionally substituted phenyl, C_{7-12}-aralkyl and optionally substituted heteroaryl; preferably Cl.

43. A synthetic method in which a compound of the formula IV or IVA



IV



IVA

in which R^2 and R^4 are as defined in claim 1;

R^{37} is selected from H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, -CN, Cl, Br, I, $-NO_2$, $-NH_2$, $-NHCOR^9$, -COOH, $-CONHR^9$, $-NHCOOR^9$ and $-COOR^9$;

R^9 is as defined in claim 1;

X^2 and Y^2 are as defined in claim 38; and

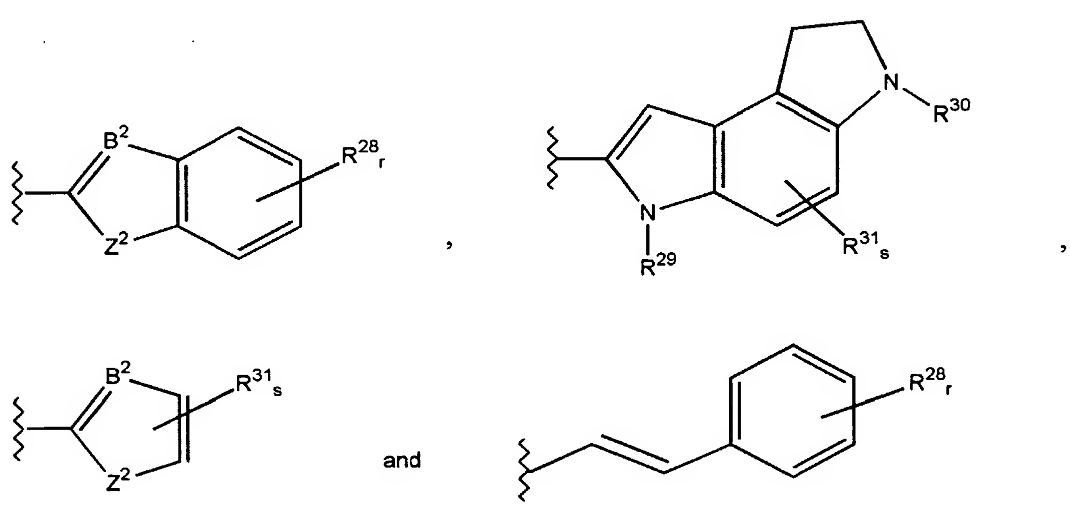
R^{26} is an amine protecting group;

is reacted with a compound of the general formula V

$R^{27}COY^3$ V

in which R^{27} is selected from C_{1-4}-alkyl, optionally substituted phenyl, C_{7-12}-aralkyl, optionally substituted heteroaryl and Ar^4;

Ar^4 is selected from



in which B^2 is N or CR^{32};

Z^2 is O, S, -CH=CH- or NR^{33};

the or each R^{28} is selected from C_{1-4}-alkoxy, C_{1-4}-alkyl, NO_2, CN, Cl, Br, $-NHR^{33}$, $-NR^{36}_2$, $-N^+R^{36}_3$-, $-NHCOR^{34}$, -COOH, $-CONHR^{35}$ and $-COOR^{35}$;

r is an integer in the range 0 to 4;

R^{29} is an amine protecting group;

R^{30} is an amine protecting group, $-CONH_2$, -COOH, $-COR^{35}$ or $-COAr^5$;

the or each R^{31} is selected from C_{1-4}-alkoxy, C_{1-4}-alkyl, NO_2, CN, Cl, Br, $-NHR^{33}$, $-NR^{36}_2$, $-N^+R^{36}_3$-, I, $-NHCOR^{34}$, -COOH, $-CONHR^{35}$ and $-COOR^{35}$;

s is 0, 1 or 2;

R^{32} is selected from H, C_{1-4}-alkoxy, C_{1-4}-alkyl, NO_2, CN, Cl, Br, I, $NHCOR^{34}$, -COOH, $-CONHR^{34}$, $-NHCOOR^{35}$ and $COOR^{34}$;

the or each R^{33} is an amine protecting group;

R^{34} is selected from Ar^5, C_{1-4}-alkyl, optionally substituted phenyl, C_{7-12}-aralkyl, optionally substituted heteroaryl and a ligand;

R^{35} is selected from C_{1-4}-alkyl, optionally substituted phenyl, C_{7-12}-aralkyl, optionally substituted heteroaryl and a ligand;

each R^{36} is selected from H, C_{1-4} alkyl, optionally substituted phenyl, C_{7-12} aralkyl and optionally substituted heteroaryl;

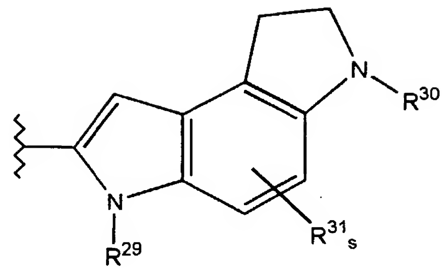
Ar^5 is selected from the same groups as Ar^4 and Y^3 is a leaving group, provided that no more than one R^{28} or R^{31} is any one ring includes a group Ar^5.

44. A method according to claim 43 which is carried out in the presence of an amide coupling reagent.

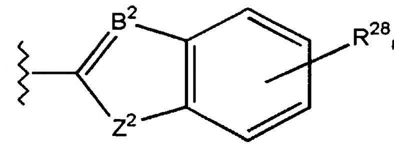
45. A method according to claim 42 or 43 in which the product is subsequently subjected to an amine deprotection step in which R^{26}, any or all groups R^{29} (if any) and/or any or all groups R^{33} (if any) are replaced by H.

46. A method according to any of claims 43 to 45 in which Y^2 is selected from $-OCOOR^5$, $-OCONHR^6$, Cl, Br, I, and $-OSOOR^7$, in which R^5, R^6 and R^7 are independently selected from C_{1-4} alkyl, optionally substituted phenyl, C_{7-12}-aralkyl and optionally substituted heteroaryl; preferably Cl.

47. A method according to any of claims 43 to 46 in which Ar^5 is

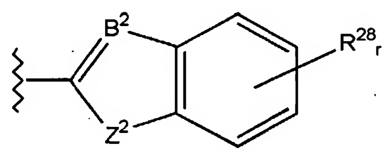


and



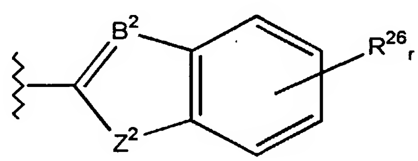
48. A method according to any of claims 43 to 47 in which R^{27} is Ar^4.

49. A method according to claim 48 in which Ar^4 is a group

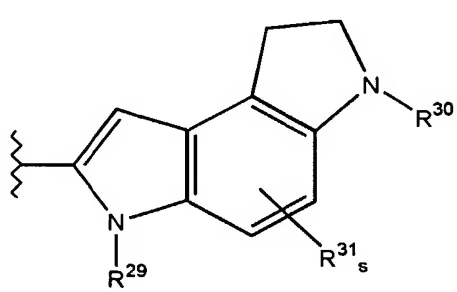


50. A method according to claim 49 in which, in R^{27}, r is at least 1 and one of the groups R^{28} is -NHCOAr^5.

51. A method according to claim 50 in which Ar^5 is

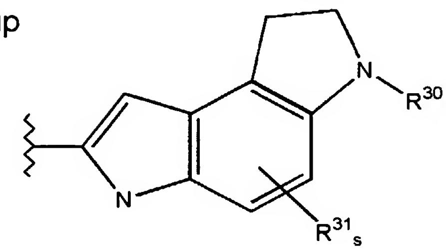


52. A method according to claim 48 in which Ar^4 is a group

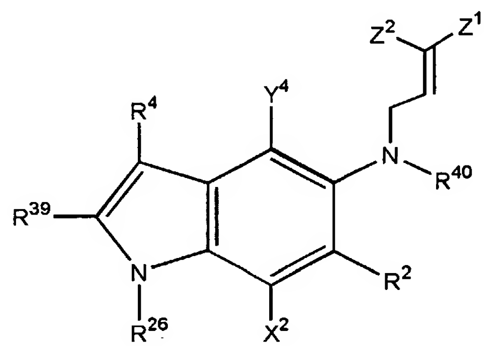


53. A method according to claim 52 in which R^{30} is -COAr^5.

54. A method according to claim 53 in which, in R^{27}, Ar^5 is a group



55. A method according to any of claims 43 to 54 in which the compound of the formula IV or IVA is produced in a preliminary step including a cyclisation step in which a compound of the general formula VI



VI

in which R^2, R^4, R^{26}, and X^2 are the same as in the compound of the formula IV;

R^{39} is the same as R^{37} or is a precursor thereof;

R^{40} is an amine protecting group different from R^{26};

one of Z^1 and Z^2 is Y^5 and the other is H;

Y^5 hydrogen, or is a leaving group which is the same as or different to Y^2; and

Y^4 is a radical leaving group

is cyclised via an arylradical-alkene cyclisation step in the presence of a catalyst.

56. A method according to claim 55 in which Z^1 is Y^2 and in which the cyclisation step is carried out in the presence of a free radical to form a dihydropyrrole ring.

57. A method according to claim 56 in which the free radical is generated from azoisobutyronitrile or is a 2,2,6,6-tetramethylpiperidinyloxy free radical.

58. A method according to claim 56 or 57 in which the catalyst is tributyl tin hydride.

59. A method according to claim 55 in which Z^2 is Y^5, Y^5 is a trialkyl tin radical, and the cyclisation step is carried out in the presence of a palladium complex to form a tetra hydroquinoline, which is oxidised to form an epoxide, the epoxide then being reduced to form an alcohol compound and, if in the product of the formula IVA, Y^2 is other than hydroxyl, the hydroxyl group of the alcohol compound is subsequently converted into Y^2.

60. A method according to any of claims 55 to 58 in which Y^4 is a halogen atom, preferably Br or I.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/00796

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/02 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 98 52925 A (SCRIPPS RESEARCH INST ;BOGER DALE L (US)) 26 November 1998 (1998-11-26) page 3, line 6 -page 7, line 16; figures 2,4,8	1-60
Y	WO 97 45411 A (SCRIPPS RESEARCH INST ;BOGER DALE L (US)) 4 December 1997 (1997-12-04) the whole document	1-60

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
7 June 2002	17/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Engl, B

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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Y	MACOR J E ET AL: "Synthesis and reactivity of pyrrolo‘3,2-e!indole: removal of a n-bom group from an unactivated indole" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 38, no. 10, 10 March 1997 (1997-03-10), pages 1673-1676, XP004054963 ISSN: 0040-4039 the whole document ---	1-59

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	MURATAKE, HIDEAKI ET AL.: "Synthesis of Duocarmycin SA by Way of Methyl 4-(Methoxycarbonyl)oxy-3H-pyrrolo'3,2-f!quinoline-2-carboxylate as a Tricyclic Heteroaromatic Intermediate" CHEMICAL & PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, TOKYO, JP, vol. 46, no. 3, 1998, page 400-412 XP001019000 the whole document ---	1-60
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International Application No
PCT/GB 02/00796

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